(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number
WO 2004/022554 A1

(51) International Patent Classification[7]: C07D 413/04, 239/70, 471/10, 487/10, 491/10, A61K 31/517, A61P 35/00

(21) International Application Number:
PCT/GB2003/003878

(22) International Filing Date:
5 September 2003 (05.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0220813.0	7 September 2002 (07.09.2002)	GB
0229186.2	14 December 2002 (14.12.2002)	GB
0312775.0	4 June 2003 (04.06.2003)	GB

(71) Applicant *(for all designated States except US)*: CELLTECH R & D LIMITED [GB/GB]; 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HAUGHAN, Alan, Findlay** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **BUCKLEY, George, Martin** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **DAVIES, Natasha** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **DYKE, Hazel, Joan** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **HANNAH, Duncan, Robert** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **MORGAN, Trevor** [GB/GB]; Celltech R & D Limited, 208 Batch Road, Slough, Berkshire SL1 3WE (GB). **RICHARD, Marianna, Dilani** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **SHARPE, Andrew** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB). **WILLIAMS, Sophie, Caroline** [GB/GB]; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

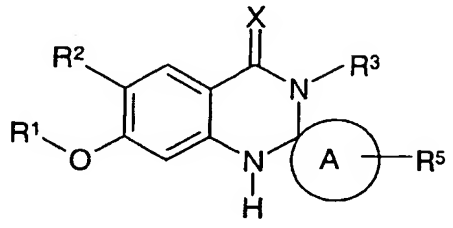
(74) Agent: **THOMPSON, John**; Celltech R & D Limited, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,

[Continued on next page]

(54) Title: QUINAZOLINONE DERIVATIVES



(I)

(57) Abstract: A compound of formula (1), wherein: X is an oxygen or sulfur atom; R^1 is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group; R^2 is an optionally substituted heteroaromatic group or a -CN group; R^3 is a group $-(Alk^1)_mL^1(Alk^2)_nR^4$ in which m and n, which may be the same or different, is each zero or the integer 1, Alk^1 and Alk^2, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^1 is a covalent bond or a linker atom or group and R^4 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; A is an optionally substituted cycloaliphatic or heterocycloaliphatic group optionally fused to an optionally substituted aryl or heteroaryl group; R^5, which may be attached to any available C or N atom present in the cycloaliphatic or heterocycloaliphatic, or where fused, aryl or heteroaryl group, is a group $-(Alk^3)_tL^2(Alk^4)_vR^6$ in which t and v, which may be the same or different, is each zero or the integer 1, Alk^3 and Alk^4, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^2 is a covalent bond or a linker atom or group and R^6 is a hydrogen or halogen atom or a -CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof. The compounds of the present invention are potent inhibitors of IMPDH.

WO 2004/022554 A1

SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

QUINAZOLINONE DERIVATIVES

This invention relates to a series of quinazolinones and quinazolinthiones and their derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Inosine-5'-monophosphate dehydrogenase (IMPDH; EC 1.1.1.205) is an enzyme involved in the *de novo* synthesis of guanine nucleotides. IMPDH catalyses the β-nicotinamide adenine dinucleotide (NAD)-dependant oxidation of inosine-5'-monophosphate (IMP) to xanthosine-5'-monophosphate (XMP) (Jackson R.C. et al., Nature, 256, pp. 331-333, (1975)). Guanine nucleotides are essential to the cell for RNA and DNA synthesis, intermediates in signalling pathways and as energy sources for metabolic pathways.

IMPDH is ubiquitous in eukaryotes, bacteria and protozoa (Y. Natsumeda & S.F. Carr, Ann. N.Y. Acad., 696, pp. 88-93, (1993)). Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced (F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et al J. Biol. Chem., 265, pp 5292-5295, (1990)). Each is 514 amino acids and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa (Y. Yamada et. Al., Biochemistry, 27, pp. 2737-2745, (1988)). It is thought that type I is the predominant isoform expressed in normal cells, whilst type II is upregulated in neoplastic and replicating cells. Studies have postulated that selective inhibition of type II IMPDH could provide a therapeutic advantage by reducing potential toxicity effects caused by inhibiting the type I isoform (Pankiewicz K.W, Expert Opin. Ther. Patents 11 (7) pp 1161-1170, (2001)).

The *de novo* synthesis of guanine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells depend on the *de novo*, rather than the salvage pathway to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen

(A.C. Allison et. al., Lancet II, 1179, (1975) and A.C. Allison et. al., Ciba Found. Symp., 48, 207, (1977)). Thus, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

Mycophenolic acid (MPA) and some of its derivatives have been described in United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 as potent, uncompetitive, reversible inhibitors of human IMPDH type I (K_i = 33 nM) and type II (K_i = 9 nM). MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen (A.C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993)).

Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases. (R.E. Morris, Kidney Intl., 49, Suppl. 53, S-26, (1996)). However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

Mycophenolate mofetil, a prodrug which quickly liberates free MPA *in vivo*, was recently approved to prevent acute allograft rejection following kidney transplantation (i.e. renal allograft failure) and heart transplantation. (L.M. Shaw, *et. al.*, Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H.W. Sollinger, Transplantation, 60, pp. 225-232, (1995); J. Kobashigawa Transplant, 66, pp. 507, (1998)). Mycophenolate mofetil has also been used for the treatment of rheumatoid arthritis. The experimental use of mycophenolate mofetil in the treatment of systemic lupus erythematosus, lupus nephritis, myasthenia gravis, inflammatory eye disease, autoimmune and inflammatory skin disorders (including psoriasis) and glomerular disease has also been described (R. Bentley, Chem. Rev., 100, pp. 3801-3825, (2000)). Mycophenolate mofetil has also been postulated to be of use for the treatment of atopic dermatitis (Grundmann-Kollman M *et al*, Archives of Dermatology, 137 (7), pp. 870-873, (2001)) and has been shown to be effective in predictive animal models of multiple sclerosis (Tran G.T *et al*, International Immunopharmacology, 1 (9-10) pp. 1709-1723, (2001)).

Several clinical observations, however, limit the therapeutic potential of this drug. (L.M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)).

Nucleoside analogues such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH (L. Hedstrom, et. al., Biochemistry, 29, pp. 849-854, (1990)). These nucleoside analogues are competitive inhibitors of IMPDH, but also inhibit other NAD dependant enzymes. This lack of specificity limits the therapeutic application of these compounds. New agents with improved selectivity for IMPDH would represent a significant improvement over these nucleoside analogues. Mizorbine (Bredinin®) has been approved in Japan for multiple indications in transplantation and autoimmune diseases including prevention of rejection after renal transplantation, idiopathic glomerulonephritis, lupus nephritis and rheumatoid arthritis.

Vertex has recently disclosed a series of novel IMPDH inhibitors (WO 97/40028), of which VX-497 has been evaluated for the treatment of psoriasis.

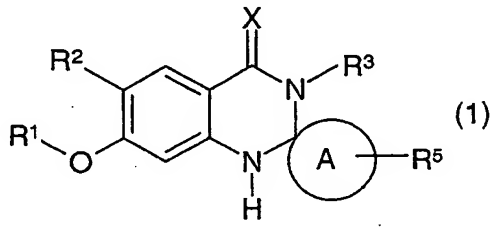
It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumour cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy (M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991), Pankiewicz K.W., Exp. Opin. Ther. Patents, 11, pp. 1161-1170, (2001)). IMPDH has also been shown to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH may be useful in preventing restenosis or other hyperproliferative vascular diseases (C.R. Gregory *et. al.*, Transplantation, 59, pp. 655-61, (1995); PCT publication WO 94/12184; and PCT publication WO 94/ 01105).

Additionally, IMPDH has been shown to play a role in viral replication in some virus-infected cell lines. (S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290, (1993)). VX-497 is currently being evaluated for the treatment of hepatitis C in humans.

Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties. Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-inflammatory agents, antipsoriatic and anti-viral agents.

The present inventors disclose a class of substituted quinazolinone and quinazolinthione derivatives having activity as IMPDH inhibitors, and to compositions and methods related thereto.

Thus we provide a compound of formula (1):



(1)

wherein:

X is an oxygen or sulfur atom;

R^1 is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R^2 is an optionally substituted heteroaromatic group or a –CN group;

R^3 is a group $-(Alk^1)_mL^1(Alk^2)_nR^4$ in which m and n, which may be the same or different, is each zero or the integer 1, Alk^1 and Alk^2, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^1 is a covalent bond or a linker atom or group and R^4 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

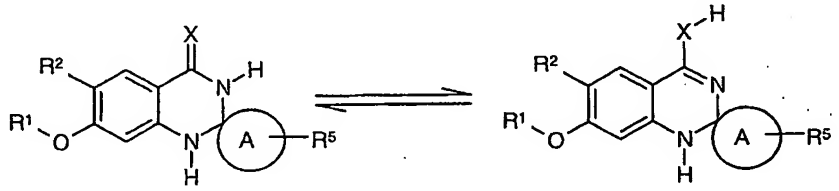
A is an optionally substituted cycloaliphatic or heterocycloaliphatic group optionally fused to an optionally substituted aryl or heteroaryl group;

R^5, which may be attached to any available C or N atom present in the cycloaliphatic or heterocycloaliphatic, or where fused, aryl or heteroaryl group, is a group $-(Alk^3)_tL^2(Alk^4)_vR^6$ in which t and v, which may be the same or different, is each zero or the integer 1, Alk^3 and Alk^4, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^2 is a covalent bond or a linker atom or group and R^6 is a hydrogen or

halogen atom or a –CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;
and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

It will be appreciated that the ring A and the rest of the molecule of formula (1) are in a spiro relationship to each other.

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers). The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$) – enol ($CH=CHOH$) tautomers. Quinazolinones may also exist as tautomers; one possible example is illustrated below:



Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

It will also be appreciated that where desired the compounds of the invention may be administered in a pharmaceutically acceptable pro-drug form, for example, as a protected carboxylic acid derivative, e.g. as an acceptable ester. It will be further appreciated that the pro-drugs may be converted *in vivo* to the active compounds of formula (1), and the invention is intended to extend to such pro-drugs. Such prodrugs are well known in the literature, see for example International Patent Application No. WO 00/23419, Bodor N. (Alfred Benson Symposium, 1982, 17, 156-177), Singh G. *et al* (J. Sci. Ind.

Res., 1996, 55, 497-510) and Bundgaard H. (Design of Prodrugs, 1985, Elsevier, Amsterdam).

In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

The term "aliphatic group" is intended to include optionally substituted straight or branched C_{1-10}alkyl, e.g. C_{1-6} alkyl, C_{2-10}alkenyl e.g. C_{2-6}alkenyl or C_{2-10} alkynyl e.g. C_{2-6}alkynyl groups.

Particular examples of aliphatic groups include optionally substituted straight or branched C_{1-6} alkyl groups such as $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, $-C(CH_3)_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, or C_{2-6}alkenyl or C_{2-6}alkynyl groups such as $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCH_2$, $-CHCHCH_2CH_3$, $-CH_2CHCHCH_3$, $-(CH_2)_2CHCH_2$, $-CCH$, $-CCCH_3$, $-CH_2CCH$, $-CCCH_2CH_3$, $-CH_2CCCH_3$, or $-(CH_2)_2CCH$ groups. More particular examples include optionally substituted C_{1-4} alkyl groups selected from $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-(CH_2)_3CH_3$ or $-C(CH_3)_3$.

The term "aliphatic chain" is intended to include those alkyl, alkenyl or alkynyl groups as just described where a terminal hydrogen atom is replaced by a covalent bond to give a divalent chain.

Examples of aliphatic chains include optionally substituted straight or branched C_{1-6} alkylene chains such as $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$,$-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH(CH_3)CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2$ or C_{2-6}alkenylene or C_{2-6}alkynylene chains such as $-CHCH-$, $-CHCHCH_2$ $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$,

-$(CH_2)_2CHCH$-, -CC-, -$CCCH_2$, -CH_2CC-, -$CCCH_2CH_2$-, -CH_2CCCH_2- or -$(CH_2)_2CCH$- chains. More particular examples include optionally substituted C_{1-3} alkylene chains selected from –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH(CH_3)CH_2$-, -$C(CH_3)_2$- and –$CH_2CH(CH_3)$- chains.

Optional substituents that may be present on the aliphatic groups or chains include those optional substituents mentioned hereinafter.

The term "heteroaliphatic chain" is intended to include the aliphatic chains just described but with each additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^3 where L^3 is a linker atom or group. Each L^3 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted –L^3CH_2-, -CH_2L^3-, -$L^3CH(CH_3)$-, -$CH(CH_3)L^3$-, -$CH_2L^3CH_2$-, -$L^3CH_2CH_2$-, -$L^3CH_2CH(CH_3)$-, -$CH(CH_3)CH_2L^3$-, -$CH_2CH_2L^3$-, -$CH_2L^3CH_2CH_2$-, -$CH_2L^3CH_2CH_2L^3$-, -$(CH_2)_2L^3CH_2$-, -$(CH_2)_3L^3CH_2$-, -$L^3(CH_2)_2CH_2$-, -L^3CH_2CHCH-, -$CHCHCH_2L^3$-, -$(CH_2)_2L^3CH_2CH_2$-, –$(CH_2)_3L^3$- and –$L^3CH_2L^3CH_2CH_2$- chains.

When L^3 is present in heteroaliphatic chains as a linker atom or group it may be any divalent linking atom or group. Particular examples include –O- or -S- atoms or –C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -$N(R^7)$- [where R^7 is a hydrogen atom or a straight or branched C_{1-6}alkyl group], -$N(R^7)O$-, -$N(R^7)N$-, -$CON(R^7)$-, -$OC(O)N(R^7)$-, -$CSN(R^7)$-, -$N(R^7)CO$-, -$N(R^7)C(O)O$-, -$N(R^7)CS$-, -$S(O)_2N(R^7)$-, -$N(R^7)S(O)_2$-, -$N(R^7)CON(R^7)$-, -$N(R^7)CSN(R^7)$, –$N(R^7)SO_2N(R^7)$-, -$C(=NOR^7)$- or -$C(R^8)$=NO- [where R^8 is a straight or branched C_{1-6}alkyl group] groups. Where L^3 contains two R^7 groups these may be the same or different.

The term "cycloaliphatic group" includes optionally substituted non-aromatic cyclic or multicyclic, saturated or partially saturated C_{3-10} ring systems, such as, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl,

adamantyl, norbornyl, norbornenyl, bicyclo[2.2.1]heptanyl or bicyclo[2.2.1]heptenyl. Particular examples include optionally substituted C_{3-6} cycloalkyl ring systems such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents present on those groups include those substituents mentioned hereinafter.

The term "cycloalkyl-alkyl- group" refers to a C_{1-6} alkyl group (as described herein) where a terminal hydrogen atom is replaced by a C_{3-6} cycloalkyl ring (as described herein). Examples include $-(CH_2)_{1-6}$-cyclopropyl, $-(CH_2)_{1-6}$-cyclobutyl, $-(CH_2)_{1-6}$-cyclopentyl or $-(CH_2)_{1-6}$-cyclohexyl.

The term "heterocycloaliphatic group" refers to an optionally substituted 3 to 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system containing one, two, three or four L^4 linker atoms or groups. Particular examples of suitable L^4 atoms or groups include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, $-N(R^7)$- [where R^7 is as defined above], $-N(R^7)N(R^7)$, $-N(R^7)O$-, $-ON(R^7)$-, $-CON(R^7)$-, $-OC(O)N(R^7)$-, $-CSN(R^7)$-, $-N(R^7)CO$-, $-N(R^7)C(O)O$-, $-N(R^7)CS$-, $-S(O)_2N(R^7)$, $-N(R^7)S(O)_2$-, $-N(R^7)CON(R^7)$-, $-N(R^7)CSN(R^7)$-, $-N(R^7)SO_2N(R^7)$- groups. Where the linker group contains two R^7 substituents, these may be the same or different. Optional substituents present on the heterocycloaliphatic groups include those substituents mentioned hereinafter.

Particular examples of heterocycloaliphatic groups include optionally substituted cyclobutanonyl, cyclopentanonyl, cyclohexanonyl, azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, oxazolidinyl, oxazolidinonyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, imidazolidinonyl, imidazolidine-2,4-dionyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, pyranonyl, piperidinyl, piperidinonyl, quinuclidinyl, 1,4-dioxanyl, morpholinyl, morpholinonyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, N-C_{1-6} alkylpiperazinyl, N-C_{1-6} alkylpyrrolidinyl, N-C_{1-6} alkylpiperidinyl, N-C_{1-6} alkylmorpholinyl,

homopiperazinyl, dihydrofuran-2-onyl, tetrahydropyran-2-onyl, isothiazolidinyl 1,1-dioxide, [1,2]thiazinanyl 1,1-dioxide, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrazolidin-3-onyl, tetrahydrothiopyranyl 1,1-dioxide, tetrahydrothiophenyl 1,1-dioxide, 1,3,5-trithianyl, oxazinyl, e.g. 2*H*-1,3-, 6*H*-1,3-, 6*H*-1,2-, 2*H*-1,2- or 4*H*-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. *o*- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, 1,3,5,-oxadiazinyl or tetrahydropyrrolo[1,2-*c*]imidazole-1,3-dionyl groups.

Cycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon atom. Heterocycloaliphatic groups may be linked to the remainder of the compound of formula (1) by any available ring carbon or, where available, ring nitrogen atom.

The optional substituents which may be present on the aliphatic, cycloaliphatic or heterocycloaliphatic groups, include one, two, three or more substituents, which each may be the same or different, selected from halogen atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, propyl or *i*-propyl, C_{1-6}alkoxy, e.g. methoxy, ethoxy or propoxy, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, C_{1-6}alkylthio, e.g. methylthio, ethylthio or propylthio, or $-(Alk^5)_gR^9$ groups in which Alk^5 is a straight or branched C_{1-3}alkylene chain, g is zero or the integer 1 and R^9 is a –OH, -SH, $-N(R^{10})_2$ [where R^{10} is a hydrogen atom or an optionally substituted C_{1-6}alkyl group], -CN, $-CO_2R^{10}$, $-OC(O)R^{10}$, $-NO_2$, $-C(O)N(R^{10})_2$, $-C(S)N(R^{10})_2$, $-C(O)R^{10}$, $-C(S)R^{10}$, $-N(R^{10})C(O)R^{10}$, $-N(R^{10})C(S)(R^{10})$, $-SO_2N(R^{10})_2$, $-N(R^{10})SO_2R^{10}$, $N(R^{10})C(O)N(R^{10})_2$, $N(R^{10})C(S)N(R^{10})_2$, $N(R^{10})SO_2N(R^{10})_2$, $-SO_2R^{10}$, $-SO_3R^{10}$, $-OCO_2R^{10}$, $-OC(O)N(R^{10})_2$ or an optionally substituted aromatic or heteroaromatic group. R^9 may also be an $-OR^{9a}$ group [where R^{9a} is an optionally substituted C_{1-6}alkyl, phenyl or 5 or 6 membered heteroaryl group]. When two R^{10} atoms or groups are present in these substituents these may be the same or different or joined to form a heterocycloaliphatic ring which contains at least one N atom. This includes, for example, azetidinyl, pyrrolidinyl, piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl,

N-C_{1-6} alkylpiperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl and the like. The aromatic and heteroaromatic groups which may be present in these substituents may optionally be substituted by one, two or three of the R^{12} groups described herein.

The optional substituents which may be present on aliphatic or heteroaliphatic chains, for example Alk^1, Alk^2, Alk^3 or Alk^4, include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, CN, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is an optionally substituted C_{1-6}alkyl group] e.g. $-CO_2CH_3$ or $-CO_2C(CH_3)_3$; $-CONHR^{11}$, e.g. $-CONHCH_3$; $-CON(R^{11})_2$, e.g. $-CON(CH_3)_2$; $-COR^{11}$, e.g. $-COCH_3$; C_{1-6}alkoxy, e.g. methoxy or ethoxy; haloC_{1-6}alkoxy, e.g. trifluoromethoxy or difluoromethoxy; -SH, $-S(O)R^{11}$, e.g. $-S(O)CH_3$; $-S(O)_2R^{11}$, e.g. $-S(O)_2CH_3$; C_{1-6}alkylthio e.g. methylthio or ethylthio; amino; $-NHR^{11}$, e.g. $-NHCH_3$ or $-N(R^{11})_2$, e.g. $-N(CH_3)_2$ groups. Where two R^{11} groups are present in any of the above substituents these may be the same or different.

When R^{9a}, R^{10} or R^{11} is present as a straight or branched C_{1-6}alkyl group it may be a straight or branched C_{1-6} alkyl group e.g. a C_{1-3} alkyl group such as methyl, ethyl or *i*-propyl. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from fluorine, chlorine, bromine or iodine atoms or hydroxy or C_{1-6} alkoxy e.g. methoxy or ethoxy groups.

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include $-CF_3$, $-CCl_3$, $-CHF_2$, $-CHCl_2$, $-CH_2F$, and $-CH_2Cl$ groups.

The term "alkoxy" as used herein is intended to include straight or branched C_{1-10}alkoxy for example C_{1-6}alkoxy such as methoxy, ethoxy, *n*-propoxy, *i*-propoxy and *t*-butoxy. "Haloalkoxy" as used herein includes any of those alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ and $-OCH_2Cl$ groups.

As used herein the term "alkylthio" is intended to include straight or branched C_{1-10}alkylthio, e.g. C_{1-6}alkylthio such as methylthio or ethylthio groups.

When L^1 and L^2 are present in compounds of formula (1) as a linker atom or group they may be any such atom or group as hereinbefore described in relation to L^3 linker atoms and groups. When m in compounds of formula (1) is zero then L^1, when present, is a -C(O)-, -C(S)-, $-S(O)_2$-, $-CON(R^7)$-, $-CSN(R^7)$- or $-S(O)_2N(R^7)$- group, where R^7 is as herein defined. Additionally L^2 may also be a $-C(O)N(R^7)C(O)$-, $-C(O)N(R^7)C(O)O$- or $-C(O)N(R^7)O$- linker group.

The terms "aromatic group" and "aryl group" are intended to include for example optionally substituted monocyclic ring C_{6-12} aromatic groups, such as phenyl, or bicyclic fused ring C_{6-12} aromatic groups, such as, 1- or 2-naphthyl groups.

The terms "heteroaromatic group" and "heteroaryl group" are intended to include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms (or oxidised versions thereof). In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-

membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Each of these aromatic or heteroaromatic groups may optionally be substituted by one, two, three or more R^{12} atoms or groups as defined below.

Particular examples of monocyclic ring heteroaromatic groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-N-oxide, dihydropyrazolonyl or imidazolonyl.

Particular examples of bicyclic ring heteroaromatic groups of this type include benzofuryl, benzothienyl, benzotriazolyl, indolyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl or phthalazinyl.

The heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

Optional substituents which may be present on the aromatic or heteroaromatic groups include one, two, three or more substituents, each selected from an atom or group R^{12} in which R^{12} is the group $-(Alk^6)_e(R^{12a})_f$ in which Alk^6 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_g-$ [where g is an integer 1 or 2] or $-N(R^{14})-$ groups; R^{12a} is a halogen atom, or an amino ($-NH_2$), $-NHR^{13}$ [where R^{13} is the group $-(Alk^6)_e(R^{13a})_f$ in which R^{13a} is an optionally substituted heterocycloaliphatic, cycloaliphatic, aryl, heteroaryl group and Alk^6, e and f are as herein defined], $-N(R^{13})_2$, nitro, cyano, amidino, formyl, hydroxy (OH), carboxyl ($-CO_2H$), $-CO_2R^{13}$, thiol (-SH), $-SR^{13}$, $-OR^{13}$,

$-COR^{13}$, $-CSR^{13}$, $-SO_3H$, $-SOR^{13}$, $-SO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NH_2$, $-SO_2NHR^{13}$, $SO_2N(R^{13})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{13}$, $-CSNHR^{13}$, $-CON(R^{13})_2$, $-CSN(R^{13})_2$, $-N(R^{14})SO_2R^{13}$, [where R^{14} is a hydrogen atom or a straight or branched C_{1-6} alkyl group] $-N(SO_2R^{13})_2$, $-N(R^{14})SO_2NH_2$, $-N(R^{14})SO_2NHR^{13}$, $-N(R^{13})SO_2N(R^{14})_2$, $-N(R^{14})COR^{13}$, $-N(R^{14})CONH_2$, $-N(R^{14})CONHR^{13}$, $-N(R^{14})CON(R^{13})_2$, $-N(R^{14})CSNH_2$, $-N(R^{14})CSNHR^{13}$, $-N(R^{14})CSN(R^{13})_2$, $-N(R^{14})CSR^{13}$, $-N(R^{14})C(O)OR^{13}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{3-7} heterocycloaliphatic group optionally containing one or more other -O- or -S- atoms or $-N(R^{14})-$, -C(O)- or -C(S)- groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{14})SO_2NHet^1$, $-N(R^{14})CONHet^1$, $-N(R^{14})CSNHet^1$, $-SO_2N(R^{14})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{3-7} cycloaliphatic group optionally containing one or more -O- or -S- atoms or $-N(R^{14})-$, -C(O)- or -C(S)- groups], $-CON(R^{14})Het^2$, $-CSN(R^{14})Het^2$, $-N(R^{14})CON(R^{14})Het^2$, $-N(R^{14})CSN(R^{14})Het^2$, optionally substituted aryl, heteroaryl, cycloaliphatic or heterocycloaliphatic group; e is zero or the integer 1 and f is zero or an integer 1, 2 or 3; provided that when e is zero then f is the integer 1. It will be further appreciated that when two R^{13} or R^{14} groups are present in one of the above substituents, the R^{13} or R^{14} groups may be the same or different.

When in the group $-(Alk^6)_e(R^{12a})_f$ or $-(Alk^6)_e(R^{13a})_f$ f is an integer 1, 2 or 3 and e is the integer 1, it is to be understood that the substituent or substituents R^{12a} or R^{13a} may be present on any suitable carbon atom in $-Alk^6$. Where more than one R^{12a} or R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^6$. It will be understood that, when f is zero and no substituent R^{12a} or R^{13a} is present the chain represented by Alk^6 contains a terminal hydrogen atom and becomes a corresponding group.

When $-NHet^1$ or $-Het^2$ forms part of a substituent R^{12a} each may be for example an optionally substituted 2- or 3-pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperazinyl, imidazolinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally

Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -$NHet^1$ or -Het^2 include those substituents described above in relation to aromatic groups.

Particularly useful atoms or groups represented by R^{12} include fluorine, chlorine, bromine or iodine, C_{1-6} alkyl, e.g. methyl, ethyl, *i*-propyl, haloC_{1-6}alkyl, e.g. -CF_3, haloC_{1-6} alkoxy, e.g. -OCF_3, -OCF_2H, -$(Alk^6)_eNH_2$, -$(Alk^6)_eNHR^{13}$, -$(Alk^6)_eN(R^{13})_2$, -$(Alk^6)_eCN$, -$(Alk^6)_eCO_2H$, -$(Alk^6)_eCO_2R^{13}$, -$(Alk^6)_eSR^{13}$, -$(Alk^6)_eOR^{13}$, -$(Alk^6)_eCOR^{13}$, -$(Alk^6)_eCSR^{13}$, -$(Alk^6)_eSO_2R^{13}$, -$(Alk^6)_eSO_2NH_2$, -$(Alk^6)_eSO_2NHR^{13}$, -$(Alk^6)_eSO_2N(R^{13})_2$, -$(Alk^6)_eCONH_2$, -$(Alk^6)_eCSNH_2$, -$(Alk^6)_eCONHR^{13}$, -$(Alk^6)_eCSNHR^{13}$, -$(Alk^6)_eCON(R^{13})_2$, -$(Alk^6)_eCSN(R^{13})_2$, -$(Alk^6)_eN(R^{14})SO_2R^{13}$, -$(Alk^6)_eN(R^{14})COR^{13}$, -$(Alk^6)_eN(R^{14})CONH_2$, -$(Alk^6)_eN(R^{14})CONHR^{13}$, -$(Alk^6)_eN(R^{14})CSR^{13}$, -$(Alk^6)_eN(R^{14})C(O)OR^{13}$, -$(Alk^6)_eSO_2NHet^1$, -$(Alk^6)_eCONHet^1$, -$(Alk^6)_eCSNHet^1$, optionally substituted -$(Alk^6)_e$phenyl, -$(Alk^6)_e$monocyclic heteroaryl, -$(Alk^6)_e$monocyclic heterocycloaliphatic or $(Alk^6)_e$cycloaliphatic.

Particularly useful R^{13} groups include a C_{1-6} alkyl group (where f is zero), or an optionally substituted -$(Alk^6)_e$phenyl, -$(Alk^6)_e$monocyclic heteroaryl, -$(Alk^6)_e$monocyclic heterocycloaliphatic or -$(Alk^6)_e$cycloaliphatic.

When Alk^6 is present in the above R^{12} and R^{13} groups it may be for example a methylene, ethylene, *n*-propylene, *i*-propylene, *n*-butylene, *i*-butylene, *s*-butylene, *t*-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -$S(O)_2$- or -$N(R^{14})$- groups. Particular examples of Alk^6 include C_{1-4} alkylene chains e.g. methylene, ethylene, propylene, i-propylene or t-butylene.

R^{13} is most especially a C_{1-3} alkyl group. R^{14} is particularly hydrogen or methyl.

When, in R^{12} or R^{13}, f is zero Alk^6 is in particular a C_{1-4} alkyl group as defined herein. When f is the integer 1, 2 or 3 Alk^6 is in particular a C_{1-3} alkylene chain.

Particular examples of aryl, heteroaryl, heterocycloaliphatic or cycloaliphatic groups which may be present in the group $-R^{12a}$ or $-R^{13a}$ include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, *N*-C_{1-6} alkylpiperazinyl, especially *N*-methylpiperazinyl, *N*-C_{1-6} alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, *N*-C_{1-6} alkylpiperidinyl, especially *N*-methylpiperidinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-*N*-oxide, dihydropyrazolonyl or imidazolonyl.

Optional substituents which may in particular be present on the aryl, heteroaryl, heterocycloaliphatic or cycloaliphatic groups represented by $-R^{12a}$ or $-R^{13a}$ include one, two, three or more atoms or groups selected from fluorine, chlorine, C_{1-3} alkoxy, especially $-OCH_3$, OCF_3, OCF_2H, CF_3, C_{1-3} alkylthio, straight or branched C_{1-3} alkyl, -CN, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, or $-COCH_3$, $-SO_2CH_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$ or CO_2H.

Where desired, two adjacent R^{12} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy or a C_{3-6} cycloalkyl or 3-10 membered monocylic heterocycloaliphatic group as defined herein.

It will be appreciated that where two or more R^{12} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulfonates, e.g. methanesulfonates, ethanesulfonates, or isothionates, arylsulfonates, e.g. *p*-toluenesulfonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In one particular group of compounds of formula (1) X is an O atom.

Examples of cycloaliphatic groups which may represent R^1 include C_{3-6} cycloalkyl groups, such as those described previously. Examples of cycloalkyl-alkyl- groups which may represent R^1 include C_{1-3} alkyl groups (as described herein) where a terminal hydrogen atom is replaced by a C_{3-6} cycloalkyl ring (as described herein), for example, cyclopropylCH_2-.

R^1, in compounds of formula (1), is in particular a C_{1-6} alkyl group. Especially preferred is when R^1 is a C_{1-3} alkyl group. Most especially preferred is when R^1 is a methyl group.

In another group of compounds of formula (1) R^1 is a haloalkyl group, especially a CHF_2 or CH_2F group.

A particularly preferred group of compounds of the invention has the formula (1) wherein R^2 is an optionally substituted monocyclic heteroaromatic group, especially a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Particular preferred heteroaromatic groups which may represent R^2 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl or pyrazolyl. Especially preferred is when R^2 is an oxazolyl group. Most especially preferred is where R^2 is an oxazol-5-yl group.

Particular examples of the group R^3, in compounds of formula (1), include –Alk^1-L^1-Alk^2-R^4, –Alk^1-L^1-R^4, –Alk^1-R^4, -L^1-Alk^2-R^4, -L^1-R^4 or -R^4 wherein Alk^1, L^1, Alk^2 and R^4 are as herein defined. One particular group of compounds of the invention has the formula (1) wherein R^3 is the group –Alk^1-L^1-R^4.

Alk^1 and Alk^2, when present in compounds of formula (1), may be the same or different and is each preferably an optionally substituted aliphatic chain, in particular a C_{1-6} alkylene chain, especially an optionally substituted –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, –$CH(CH_3)CH_2$- or –$CH_2CH(CH_3)$- chain, most especially a C_{1-3} alkylene chain such as –CH_2-, –CH_2CH_2- or -$CH_2CH_2CH_2$- chain.

Particular examples of L^1, when present in compounds of formula (1), include –O- or -S- atoms or –C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -$N(R^7)$- [where R^7 is as defined hereinbefore], -$CON(R^7)$-, -$CSN(R^7)$-, -$N(R^7)CO$-, -$N(R^7)CS$-, -$S(O)_2N(R^7)$- or -$N(R^7)S(O)_2$- groups. R^7 is especially a hydrogen atom or a C_{1-3} alkyl group, particularly methyl.

L^1 in one particular group of compounds of the invention is a covalent bond.

One particular class of compounds of the invention has the formula (1) wherein R^3 is the chain $-Alk^1-L^1-R^4$ in which Alk^1 is an optionally substituted aliphatic chain, L^1 is a covalent bond and R^4 is a hydrogen atom. In one particular group of compounds of this class R^3 is especially a straight or branched C_{1-6} alkyl group, particularly $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CH_3$ or $-C(CH_3)_3$. In this group of compounds R^3 is preferably a methyl or ethyl group, most especially a methyl group.

Another class of compounds of the invention has the formula (1) wherein R^3 is a hydrogen atom.

In one particular embodiment of the invention R^3 is a hydrogen atom or a C_{1-6}alkyl group, particularly methyl.

In one group of compounds of the invention A is an optionally substituted, optionally fused C_{3-6} cycloaliphatic group or 3 to 6 membered saturated monocyclic hydrocarbon ring system containing one or two L^4 linker atoms or groups. Particular examples of suitable L^4 atoms or groups include -O- or -S- atoms or $-C(O)-$, $-C(S)-$, $-S(O)_2-$, $-N(R^7)-$ [where R^7 is as defined above], $-CON(R^7)-$, $-CSN(R^7)-$, $-N(R^7)CO-$, $-N(R^7)CS-$, $-S(O)_2N(R^7)$, $-N(R^7)S(O)_2-$, groups. Particular examples of the group A include optionally substituted cyclopentyl, cyclopentenyl, cyclohexyl, cyclopentanonyl, cyclohexanonyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperidinonyl, *N*-C_{1-6} alkylpyrrolidinyl, *N*-C_{1-6} alkylpiperidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl 1,1-dioxide or tetrahydrothiophenyl 1,1-dioxide.

More particular examples of the group A include optionally substituted cyclopentyl, cyclohexyl, cyclopentanonyl, cyclohexanonyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperidinonyl, *N*-C_{1-6} alkylpyrrolidinyl or *N*-C_{1-6} alkylpiperidinyl. A is in particular an optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl,

pyrrolidinyl, piperidinyl, *N*-C_{1-6} alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, or *N*-C_{1-6} alkylpiperidinyl, especially *N*-methylpiperidinyl group.

In another particular group of compounds of formula (1) A is an optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, tetrahydrothiophenyl or tetrahydrothiophenyl 1,1-dioxide group. Typical examples of A include optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, pyrrolidin-2-on-3-yl, piperidin-4-yl, tetrahydrothiophen-3-yl or tetrahydrothiophen-3-yl 1,1-dioxide group.

One particular class of compounds of the invention has the formula (1) wherein A is an optionally substituted cycloaliphatic or heterocycloaliphatic group fused to an optionally substituted aryl or heteroaryl group.

Particular examples of aryl or heteroaryl groups which may be fused to the group A include optionally substituted monocyclic C_{6-12}aromatic groups, such as phenyl or optionally substituted monocyclic C_{1-9}heteroaromatic groups, especially 5 or 6 membered heteroaromatic groups, containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms as defined hereinbefore.

One particular group of aryl or heteroaryl groups which may be fused to the group A include optionally substituted phenyl, pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or pyridyl-*N*-oxide. More particular examples include optionally substituted imidazolyl, *N*-C_{1-6}alkylimidazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or pyridyl-N-oxide.

In one particular class of compounds of the invention A is an optionally substituted cyclopentyl, tetrahydrofuranyl, pyrrolidinyl, N-C_{1-6} alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, group fused to an optionally substituted imidazolyl, *N*-C_{1-6}alkylimidazolyl, phenyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or pyridyl-*N*-oxide group. In one group of compounds of the

invention A forms an optionally substituted indanyl group. A may also in particular be an optionally substituted 5,6-dihydro-4H-cyclopenta[b]thiophenyl or tetrahydronaphthyl group. Typical examples of A include indan-1-yl, indan-2-yl, 5-nitroindan-2-yl, 5-aminoindan-2-yl, 5-*tert*-butoxycarbonylaminoindan-2-yl, 5,6-dihydro-4H-cyclopenta[b] thiophen-5-yl or 1,2,3,4-tetrahydronaphth-2-yl groups.

Particular examples of the group R^5, in compounds of formula (1), include $-Alk^3-L^2-Alk^4-R^6$, $-Alk^3-L^2-R^6$, $-Alk^3-R^6$, $-L^2-Alk^4-R^6$, $-L^2-R^6$ or $-R^6$ wherein Alk^3, L^2, Alk^4 and R^6 are as herein defined.

In one particular embodiment of the invention t is zero. In another particular embodiment of the invention t is the integer 1.

v in one particular aspect of the invention is zero. In another embodiment v is the integer 1.

Alk^3 and Alk^4, when present in compounds of formula (1), may be the same or different and is each preferably an optionally substituted aliphatic chain, in particular a C_{1-6} alkylene chain, most especially a C_{1-3} alkylene chain.

Alk^3 in one particular group of compounds of the invention is a $-CH_2-$ chain.

Particular examples of Alk^4 in compounds of the invention include $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$ or $-(CH_2)_2C(CH_3)_2CH_2-$ chains.

Optional substituents which may in particular be present on Alk^3 and/ or Alk^4 include –CN, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6}alkoxy, particularly methoxy or ethoxy; haloC_{1-6}alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$, groups. R^{11} is in particular a C_{1-3} alkyl group.

Particular examples of L^2, when present in compounds of formula (1), include –O- or -S- atoms or –C(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -C(O)O-, -OC(O)-, -$N(R^7)$- [where R^7 is as defined hereinbefore], -$CON(R^7)$-, -$CSN(R^7)$-, -$N(R^7)CO$-, -$N(R^7)CS$-, -$S(O)_2N(R^7)$- or -$N(R^7)S(O)_2$- groups. L^2 may also, in particular, be a -$N(R^7)C(O)O$-, –$C(O)N(R^7)C(O)$- or –$C(O)N(R^7)O$- group. R^7 is especially a hydrogen atom or a C_{1-3} alkyl group, particularly methyl. Typical examples of L^2 include –C(O)-, -$S(O)_2$-, -C(O)O-, -CON(H)-, -$CON(CH_3)$-, -$CON(CH_2CH_3)$-, -$CON(CH(CH_3)_2)$-, -N(H)CO-, -N(H)C(O)O-, –C(O)N(H)C(O)- or –$C(O)N(CH_3)O$-.

L^2 in one particular group of compounds of the invention is a covalent bond.

R^6 in compounds of formula (1) is in particular a hydrogen or halogen atom or an optionally substituted C_{3-6} cycloalkyl, 5 to 7 membered heterocycloalkyl, phenyl or a 5 to 10 membered heteroaryl group.

Particular R^6 examples include hydrogen or fluorine or optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, *N*-C_{1-6} alkylpiperazinyl, especially *N*-methylpiperazinyl, *N*-C_{1-6} alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, *N*-C_{1-6} alkylpiperidinyl, especially *N*-methylpiperidinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-*N*-oxide, benzofuryl, benzothienyl or indolyl. More particular examples include optionally substituted cyclopropyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, isoxazolyl, pyridyl, pyrimidinyl, benzofuryl or benzothienyl.

Typical values of R^6 include hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, pyrrolidin-1-yl, piperidin-1-yl, piperidin-4-yl, 1-(*tert*-butoxycarbonyl)piperidin-4-

yl, 1-acetylpiperidin-4-yl, 4-(4-chlorophenoxy)piperidin-1-yl, 4-trifluoromethylpiperidin-1-yl, 4-(2-fluorophenyl)piperidin-1-yl, 4-(pyridyl-4-oxy)piperidin-1-yl, 4-(benzofur-2-yl)piperidin-1-yl, 4-methylpiperazin-1-yl, 4-(*tert*-butoxycarbonyl)piperazin-1-yl, morpholin-1-yl, tetrahydropyran-4-yl, phenyl, 3-aminophenyl, 3-aminomethylphenyl, 3-[(*tert*-butoxycarbonyl)aminomethyl]phenyl, 3-[(tetrahydrofur-3yloxycarbonyl)aminomethyl]phenyl, 2-fluorophenyl, 2,4-difluorophenyl, 2-chlorophenyl, 2-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 4-methoxycarbonylphenyl, 4-carboxyphenyl, 4-methoxyphenyl, pyrrol-2-yl, 1-methylpyrrol-2-yl, fur-2-yl, 5-[4-(trifluoromethyl)phenyl]fur-2-yl, fur-3-yl, thien-3-yl, 1-methylimidazol-2-yl, 3,5-dimethylisoxazol-4-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-2-yl or benzothien-3-yl.

One class of compounds of the invention has the formula (1) wherein R^5 is the chain $-Alk^3-L^2-R^6$ in which Alk^3 is an optionally substituted aliphatic chain, L^2 is a covalent bond and R^6 is a hydrogen atom. Alk^3 in compounds of this type is preferably a straight or branched C_{1-6} alkylene chain as herein defined, especially $-CH_2-$, $-CH_2CH_2-$, $-(CH_2)_2CH_2-$, $-(CH_2)_3CH_2-$ or $-CH_2C(CH_3)_2-$. Optional substituents present on these chains include those as herein defined for Alk^3 substituents, especially –CN, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6} alkoxy, particularly methoxy or ethoxy; haloC_{1-6}alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$ groups. R^{11} is in particular a C_{1-3} alkyl group. In one particular group of compounds of this type Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$ chain substituted with a $-NH(CH_3)$, $-N(CH_3)_2$, –CN, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, $-CONH_2$, $-CONHCH_3$ or $-CON(CH_3)_2$ group. Typical examples of R^5 in compounds of this type include methyl, $-(CH_2)_2C(CH_3)_3$, $-CH_2CO^tBu$ or $-CH_2CON(CH_3)_2$.

Another class of compounds of the invention has the formula (1) wherein R^5 is the chain $-Alk^3-L^2-R^6$ in which Alk^3 is an optionally substituted aliphatic chain, L^2 is a covalent bond or a linker atom or group and R^6 is an optionally

substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group especially an optionally substituted heterocycloaliphatic, aromatic or heteroaromatic group. Alk^3 in compounds of this type is in particular an optionally substituted C_{1-6} alkylene chain, especially $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$. R^6 in compounds of this type is especially an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. Particular R^6 examples include optionally substituted azetidinyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, *N*-C_{1-6} alkylpiperazinyl, especially *N*-methylpiperazinyl, *N*-C_{1-6} alkylpyrrolidinyl, especially *N*-methylpyrrolidinyl, *N*-C_{1-6} alkylpiperidinyl, especially *N*-methylpiperidinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, pyridyl-*N*-oxide, dihydropyrazolonyl or imidazolonyl. A typical example of R^5 in compounds of this type includes $-CH_2$phenyl.

In another class of compounds of the invention R^5 is the chain $-L^2-(Alk^4)_v-R^6$ in which L^2 is a linker atom or group, Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain, v is zero or the integer 1 and R^6 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, as defined herein.

Alk^4 in compounds of this class is preferably an optionally substituted straight or branched C_{1-6} alkylene chain as defined herein or a $-CH_2L^3-$ [where L^3 is as defined herein], $-CH(CH_3)L^3-$, $-CH_2L^3CH_2-$, $-CH(CH_3)CH_2L^3-$, $-CH_2CH_2L^3-$, $-CH_2L^3CH_2CH_2-$, $-(CH_2)_2L^3CH_2-$, $-(CH_2)_3L^3CH_2-$ or $-(CH_2)_3L^3-$ chain, most especially a C_{1-6} alkylene chain. R^6 is preferably a hydrogen atom or an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. In one group of compounds of this class L^2 is in particular $-O-$, $-N(R^7)-$, $-C(O)-$, $-C(S)-$, $-S(O)_2-$, $-C(O)O-$, $-OC(O)-$, $-CON(R^7)-$, $-CSN(R^7)-$, $-N(R^7)CO-$ or $-N(R^7)CS-$,

[where R^7 is especially a hydrogen atom or a methyl group] and Alk^4 is most preferably an optionally substituted C_{1-3} alkylene chain, especially $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$. In another particular group of compounds of this class L^2 is a $-C(O)-$, $-C(O)O-$, $-S(O)_2-$, $-CON(R^7)$, $-N(R^7)C(O)O-$ or $-C(O)N(R^7)CO-$ group. Optional substituents which may in particular be present on Alk^4 include $-CN$, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6}alkoxy, particularly methoxy or ethoxy; haloC_{1-6}alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$, groups. R^{11} is in particular a C_{1-3} alkyl group.

Another class of compounds has the formula (1) wherein R^5 is the group R^6. In compounds of this class R^6 is in particular a halogen atom a $-CN$ group or an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. A typical example of R^6 in compounds of this type includes pyrid-2-yl.

In another class of compounds of the invention R^5 is the chain $-Alk^3-L^2-Alk^4-R^6$ in which Alk^3 is an optionally substituted aliphatic chain, L^2 is a linker atom or group, Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain and R^6 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group.

One particular group of compounds according to the invention has the formula (1) wherein R^5 is a C_{1-6} alkyl group, especially a C_{1-3} alkyl group, most especially a methyl group.

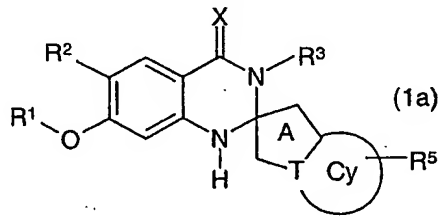
Another particular group of compounds of the invention has the formula (1) wherein R^5 is a hydrogen atom.

One group of cycloaliphatic or heterocycloaliphatic substituents, which may be present on the groups A, R^4 or R^6, are one, two, three or more groups selected from C_{1-3} alkoxy, OCF_3, OCF_2H, CF_3, C_{1-3} alkylthio, optionally substituted straight or branched C_{1-3} alkyl (wherein the optional alkyl substituent is in

particular an optionally substituted phenyl or monocyclic heteroaromatic group), optionally substituted phenyl or monocyclic heteroaromatic group, -CN, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, or $-COCH_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$ or CO_2H. Further substituents, which may in particular be present on R^6, include *tert*-butoxycarbonyl, optionally substituted phenoxy e.g. 4-chlorophenoxy, pyridyloxy e.g. pyrid-4-yloxy.

One group of aromatic or heteroaromatic substituents, which may be present on the groups R^4 or R^6, or the aryl or heteroaryl group optionally fused to the group A, are one, two, three or more atoms or groups selected from fluorine, chlorine, straight or branched C_{1-6} alkyl, optionally substituted morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, methoxy, OCF_3, OCF_2H, CF_3, CN, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2CH_3, $CO_2CH_2CH_3$, $-CO_2C(CH_3)_3$, or $-COCH_3$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-SCH_3$, $-SO_2CH_3$ or CO_2H.

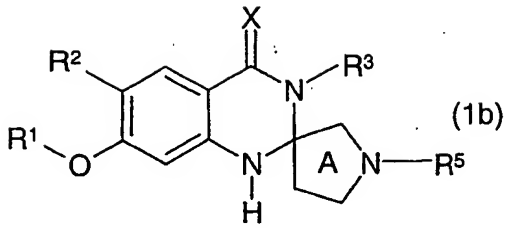
One particular class of compounds of the invention has the formula (1a):



(1a)

in which A is an optionally substituted cyclopentyl ring fused to a group Cy in which Cy is an optionally substituted phenyl or monocyclic C_{1-9}heteroaromatic group, especially a 5 or 6 membered heteroaromatic group, containing for example one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen atoms as defined hereinbefore; T is a carbon or nitrogen atom; R^1, R^2, R^3, R^5 and X are as defined and further defined for compounds of formula (1).

Another particular class of compounds of the invention has the formula (1b):



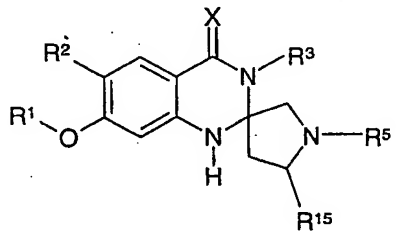
in which A is an optionally substituted pyrrolidinyl ring; R^1, R^2, R^3, R^5 and X are as defined and further defined for compounds of formula (1).

In one particular class of compounds of formula (1b) R^5 is a group $-L^2-(Alk^4)_v-R^6$ in which L^2 is a linker atom or group, Alk^4 is an optionally substituted aliphatic or heteroaliphatic chain, v is zero or the integer 1 and R^6 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, as defined herein. Alk^4 in compounds of this type is preferably an optionally substituted straight or branched C_{1-6} alkylene chain as defined herein or a $-CH_2L^3-$ [where L^3 is as defined herein], $-CH(CH_3)L^3-$, $-CH_2L^3CH_2-$, $-CH(CH_3)CH_2L^3-$, $-CH_2CH_2L^3-$, $-CH_2L^3CH_2CH_2-$, $-(CH_2)_2L^3CH_2-$, $-(CH_2)_3L^3CH_2-$ or $-(CH_2)_3L^3-$ chain, most especially a C_{1-6} alkylene chain. R^6 is preferably a hydrogen atom or an optionally substituted C_{3-6} cycloalkyl, 3-10 membered saturated monocyclic heterocycloaliphatic, phenyl or monocyclic heteroaromatic group. In one group of compounds of this class L^2 is in particular $-C(O)-$, $-C(S)-$, $-S(O)_2-$, $-C(O)O-$, $-CON(R^7)-$ or $-CSN(R^7)-$ [where R^7 is especially a hydrogen atom or a methyl group] and Alk^4 is most preferably an optionally substituted C_{1-3} alkylene chain, especially $-CH_2-$, CH_2CH_2- or $-CH_2CH_2CH_2-$. In another particular group of compounds of this class L^2 is a $-C(O)-$, $-C(O)O-$, $-S(O)_2-$, $-CON(R^7)$, $-N(R^7)C(O)O-$ or $-C(O)N(R^7)CO-$ group. Optional substituents which may in particular be present on Alk^4 include $-CN$, $-CO_2H$, $-CO_2R^{11}$ [where R^{11} is as herein defined] $-CONHR^{11}$, $-CON(R^{11})_2$, $-COR^{11}$, C_{1-6}alkoxy, particularly methoxy or ethoxy; haloC_{1-6}alkoxy, particularly trifluoromethoxy or difluoromethoxy; $-S(O)R^{11}$, $-S(O)_2R^{11}$, amino, $-NHR^{11}$ or $-N(R^{11})_2$, groups. R^{11} is in particular a C_{1-3} alkyl group.

One particular group of compounds of this type has the formula (1b) wherein L^2 is a linker group selected from $-C(O)-$, $-C(S)-$, $-S(O)_2-$, especially $-C(O)-$, v

is zero and R^6 is an optionally substituted 3-10 membered saturated monocyclic heterocycloaliphatic group which contains one or more N atoms or groups, wherein the heterocycloaliphatic group is attached to the group L^2 through any available N atom. Particular examples of R^6 groups of this type include optionally substituted azetidinyl, pyrrolidinyl, piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl, *N*-C_{1-6} alkylpiperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl or oxazolidinyl, especially optionally substituted pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl.

A further particular class of compounds of the invention has the formula (1c):



(1c)

wherein R^1, R^2, R^3, R^5 and X are defined for compounds of formulae (1) and (1b); R^{15} is a group selected from –CN, $-CO_2R^{10a}$ [where R^{10a} is a hydrogen atom or a C_{1-6}alkyl group], $-AlkOR^{10a}$ [where Alk is a C_{1-3}alkylene chain], $-NR^{10a}COR^{16}$ [where R^{16} is a C_{1-6}alkyl group], $-NR^{10a}SO_2R^{16}$, $-SO_2R^{16}$, $-COR^{16}$, $-CONR^{17}R^{18}$ [where R^{17} and R^{18}, which may be the same or different, is each a hydrogen atom or a C_{1-6}alkyl group, or R^{17} and R^{18} may join together to form a 4 to 6 membered heterocycloalkyl group], $-NR^{17}R^{18}$, $-SO_2NR^{17}R^{18}$, C_{1-6}alkyl, haloC_{1-6}alkyl or 5 or 6 membered heteroaryl group.

R^{15} in one particular group of compounds of formula (1c) is selected from –CN, $-CO_2R^{10a}$, $-AlkOR^{10a}$, $-NR^{10a}COR^{16}$, $-CONR^{17}R^{18}$, $-NR^{17}R^{18}$, or optionally substituted C_{1-6}alkyl or 5 or 6 membered heteroaryl group.

In one particularly preferred group of compounds of formula (1c) R^{15} is selected from –CN, $-CO_2R^{10a}$, $-AlkOR^{10a}$, $-CONR^{17}R^{18}$, or a 5 or 6 membered heteroaryl group. One particularly preferred group of compounds has the formula (1c) wherein R^{15} is a $-CO_2R^{10a}$ or $-CONR^{17}R^{18}$ group.

Particular C_{1-6} alkyl groups, which may represent the groups R^{10a}, R^{16}, R^{17} or R^{18} in compounds of formula (1c), include methyl, ethyl, propyl or isopropyl.

Alk in compounds of formula (1c) is preferably a C_{1-3} alkylene chain, especially methylene or ethylene.

Particular heterocycloalkyl groups, which may represent $NR^{17}R^{18}$, include 4 – 6 membered heterocycloalkyl groups selected from azetidinyl, pyrrolidinyl, piperidinyl, imidazolidinyl, thiazolidinyl, pyrazolidinyl, piperazinyl, *N*-C_{1-6} alkylpiperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, most particularly pyrrolidinyl.

Particular heteroaryl groups which may represent R^{15} include optionally substituted 5 membered groups selected from pyrrolyl, furyl, thienyl, imidazolyl, *N*-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl or tetrazolyl, especially 3-methyl oxadiazolyl.

Typical examples of the group R^{15} include $-CO_2CH_3$, $-CO_2CH(CH_3)_2$, $-CO_2H$, $CON(CH_3)_2$, -C(O)pyrrolidin-1-yl or 3-methyloxadiazolyl.

Typical examples of R^5 in compounds of formula (1c) include H, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH(CH_3)_2$, $-CO_2C(CH_3)_3$, -C(O)fur-2-yl, -C(O)piperidin-1-yl, $-CON(CH_3)$phenyl or $-C(O)N(CH_3)OCH_3$.

Compounds of formula (1) are potent inhibitors of IMPDH. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

Thus the compounds of the invention may be used in the treatment of IMPDH-associated disorders. The invention extends to such a use and in general to the use of the compounds of formula (1) for the manufacture of a medicament for treating such diseases and disorders.

"IMPDH-associated disorders" refers to any disorder or disease state in which inhibition of the enzyme IMPDH (inosine monphosphate dehydrogenase, EC1.1.1.205, of which there are presently two known isozymes referred to as IMPDH type 1 and IMPDH type 2) would modulate the activity of cells (such as lymphocytes or other cells) and thereby ameliorate or reduce the symptoms or modify the underlying cause(s) of that disorder or disease. There may or may not be present in the disorder or disease an abnormality associated directly with the IMPDH enzyme. Examples of IMPDH-associated disorders include transplant rejection and autoimmune disorders, such as rheumatoid arthritis, lupus, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory disorders, cancer and tumors, T-cell mediated hypersensitivity diseases, ischemic or reperfusion injury, viral replication diseases, proliferative disorders and vascular diseases.

Use of the compounds of the present invention is exemplified by, but is not limited to, treating a range of disorders such as: treatment of transplant rejection (e.g. kidney, liver, heart, lung, pancreas (e.g., islet cells), bone marrow, cornea, small bowel, skin allografts, skin homografts (such as employed in burn treatment), heart valve xenografts, serum sickness, and graft vs. host disease, in the treatment of autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (such as Crohn's disease and ulcerative colitus), pyoderma gangrenum, lupus (systemic lupus erythematosis), myasthenia gravis, psoriasis, eczema, dermatitis, dermatomyosis, atopic dermatitis; multiple sclerosis, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome) glomerulonephritis, scleroderma, morphea, lichen planus, viteligo (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, cicatricial pemphigoid, Gullivan-Barre syndrome, and alveolitis; in the treatment of T-cell mediated hypersensitivity

diseases, including contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis (including that due to poison ivy), urticaria, skin allergies, respiratory allergies (hayfever, allergic rhinitis) and gluten-sensitive enteropathy (Celiac disease); in the treatment of inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, acute respiratory distress syndrome, Sezary's syndrome and vascular diseases which have an inflammatory and or a proliferatory component such as restenosis, stenosis and artherosclerosis; in the treatment of cancer and tumor disorders, such as solid tumors, lymphomas and leukemia; in the treatment of fungal infections such as mycosis fungoides; in protection from ischemic or reperfusion injury such as ischemic or reperfusion injury that may have been incurred during organ transplantation, myocardial infarction, stroke or other causes; in the treatment of DNA or RNA viral replication diseases, such as herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, Epstein-Barr, human immundeficiency virus (HIV) and influenza.

Additionally, IMPDH is also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds of the present invention may be useful in treatment or prevention of bacterial infection, alone or in combination with other antibiotic agents.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the afore mentioned exemplary disorders irrespective of their etiology, for example, for the treatment of lupus, psoriasis, inflammatory bowl disease, multiple sclerosis, atopic dermatitis, transplant rejection or rheumatoid arthritis.

In another particular embodiment the compounds of the present invention are of particular use for the treatment of DNA or RNA viral replication diseases, such as hepatitis (including hepatitis B and hepatitis C) cytomegalovirus, human immundeficiency virus (HIV) and influenza.

In an additional particular embodiment the compounds of the present invention are of particular use for the treatment of cancer and tumour disorders, such as solid tumors, lymphoma, leukemia and other forms of cancer.

The compounds of formula (1) can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, anti-inflammatory agents, antibiotics, anticancer agents and immunosuppressants.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Alternate compositions of this invention comprise a compound formula (1) or a salt thereof; an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, anti-fungal agent, anti-vascular hyperproliferation agent or an antibiotic agent; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

Thus, for example, additional immunosuppression agents include, but are not limited to, cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, OKT3, ATAG, interferon and mizoribine. Additional anti-cancer agents include, but are not limited to, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioxantheres. Additional anti-viral agents include, but are not limited to, Cytovene, Ganiclovir, trisodium phosphonoformate, Ribavirin, d4T, ddI, AZT and acyclovir. Additional anti-vascular hyperproliferative agents include, but are not limited to, HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic acid, ciprostene, trapidil, ACE inhibitors, low molecular weight heparin, and rapamycin.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physician's Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, vaginal or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds of formula (1) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds of formula (1) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for example cocoa butter and polyethylene glycols.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

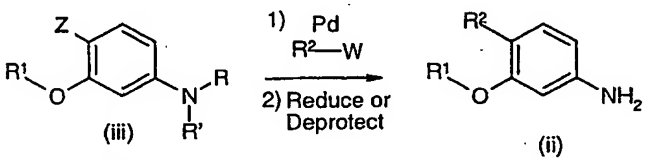
In the following process description, the symbols R^1, R^2, R^3, R^4 and R^5 when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. It will be appreciated that the syntheses described herein for the preparation of compounds of formula (1) also apply to the compounds of formulae (1a), (1b) and (1c), unless otherwise stated.

Compounds of formula (1) may be prepared according to one of several general methods, including the method shown in Scheme D, below.

An appropriate starting material for the preparation of compounds of formula (1) is an amine of formula (ii), as shown below.

Amines of general formula (ii) may be prepared in a variety of ways. For example, the amine of formula (ii) where R^1 is a methyl group and R^2 is an oxazole group may be prepared using methods known in the literature (CAS 198821-79-3).

Alternatively amines of formula (ii), where R^2 is an optionally substituted heteroaromatic group, may be prepared using the route as shown in Scheme A:



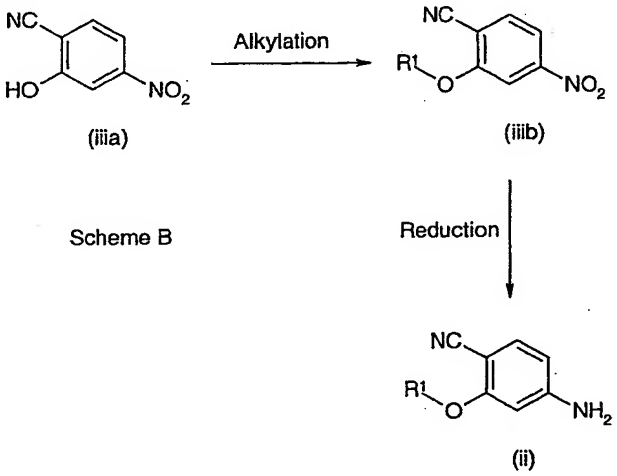
Z=Cl, Br or OTf
R=R'=H or R=R'=O
or R=H, R'=Protecting group

Scheme A

For example, a compound of formula (iii), where Z is a halogen atom e.g. Cl or Br or a suitable leaving group e.g. trifluoromethylsulfonyloxy (OTf) and –NRR' is a nitro group or an amine group (which may be suitably protected), may be reacted with a derivative of the desired heteroaromatic group (R^2-W, where W is as described below) utilising a palladium catalysed cross coupling reaction. The following literature methodology may be used to perform this coupling reaction according to the nature of the W group; e.g. when W is a hydrogen atom (Heterocycles, 31, pp. 1951-1958, (1990)); the zinc species (W=ZnCl) (J Organomet. Chem., 390, pp. 389-398, (1990); Tetrahedron, 53, pp. 7237-7254, (1997)); the mercury species (W=HgBr) (Chem. Heterocycl. Compd., 19, pp. 1159-1162, (1983)) or a boron derivative ($W=B(OH)_2$, $W=BEt_2$) (J. Med. Chem., 40, pp. 3542-3550, (1997); J. Org. Chem., 63, pp. 8295-8303, (1998)). The resulting coupled product may require further manipulation, depending on the nature of the –NRR' group, in order to obtain an amine of formula (ii). For example, when –NRR' is a nitro group this may be reduced to

an amine using standard techniques such as those methods as described hereinafter, or when –NRR' is a protected amine the protecting group may be removed using standard methodology, for example a carbamate protecting group e.g. *tert*-butoxycarbonyl may be removed under acidic conditions e.g. trifluoroacetic acid. It will be appreciated that the various R^2-W derivatives are either commercially available or may be prepared using methods known to those skilled in the art. In a similar manner the compounds of formula (iii) are either commercially available or may be prepared using methods known to those skilled in the art. For example, the compound of formula (iii) may be prepared by alkylation of the phenol precursor of (iii) using standard techniques.

Further, when R^2 is a CN group amines of formula (ii) may be prepared from 2-hydroxy-4-nitrobenzonitrile (iiia) (CAS 39835-14-8) as shown in the general Scheme B below:

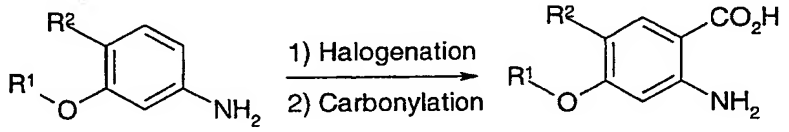


(iiia) (iiib) (ii)

Scheme B

Thus a phenol of formula (iiia) may be alkylated using conditions known to those skilled in the art, typically using an alkyl halide e.g. iodoethane and sodium hydride in *N,N*-dimethylformamide, to give an ether of formula (iiib). Alternatively these compounds may be commercially available, for example R^1=Me (CAS 101084-96-2). The compound of formula (iiib) may then be reduced to give the desired amine of formula (ii) using standard methods, for example hydrogenolysis using palladium catalysis.

The amine of formula (ii) may then be converted to an amino acid of general formula (iv) using a two-step process as shown in Scheme C. Thus an amine of formula (ii) may be treated with a halogen source such as bromine or a halosuccinimide e.g. chloro or bromosuccinimide. The reaction may be performed in a solvent such as acetonitrile or an ether e.g. a cyclic ether such as tetrahydrofuran at a temperature from about 0° to 30°. When bromine is used as halogen source the reaction may optionally be performed in the presence of added base such as an amine e.g. triethylamine. The intermediate thus formed may be converted into a carboxylic acid of formula (iv) using methods known to those skilled in the art. For example the halogenated intermediate may be treated with carbon monoxide under pressure in the presence of a catalyst e.g. a palladium catalyst such as dichlorobis(triphenylphosphene)palladium(II) in for example water and an appropriate solvent e.g *N,N*-dimethylformamide or tetrahydrofuran. It may be appropriate to carry out the reaction at an elevated temperature, such as 90-100°C.

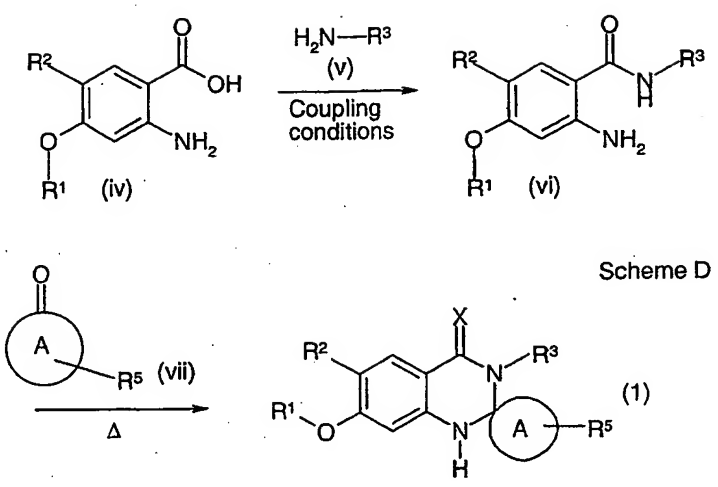


(ii) (iv)

Scheme C

Amino acids of formula (iv) may also be known compounds (e.g. R^1=Me, R^2=Oxazole; CAS 371251-38-6).

In one aspect of the invention quinazolinones of formula (1) may be prepared by reacting an amine of formula (vi) with a carbonyl compound of formula (vii). Thus, quinazolinones of formula (1) may be prepared using the general route as shown in Scheme D:



Scheme D

Thus amino acids of formula (iv) may be reacted with amines of formula (v) using coupling reaction conditions familiar to those skilled in the art to give amides (vi). For example, an acid of formula (iv) may be activated *in situ* using for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), advantageously in the presence of a catalyst such as a *N*-hydroxy compound, e.g. *N*-hydroxybenzotriazole, using suitable conditions, e.g. in *N,N*-dimethylformamide, prior to the subsequent addition of an amine of formula (v). A base such as an amine base e.g. triethylamine or diisopropylethylamine may also be employed in the reaction. Alternatively acids of formula (iv) may be reacted with oxalyl chloride in an inert solvent (such as dichloromethane) to give an intermediate acid chloride, which may or may not be isolated, but which in turn is reacted with an amine of formula (v) at a suitable temperature such as room temperature to give the amide (vi). The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or *N*-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide at for example ambient temperature.

Amines of formula (v) may be commercially available, known compounds in the literature or may be prepared using methods known to those skilled in the art.

Formation of quinazolinones of formula (1) may be achieved by condensation of amino amides (vi) with aldehydes or ketones of formula (vii) typically using acid, e.g *p*-toluenesulfonic acid, catalysed conditions similar to those employed by Bhavani and Reddy (Org. Prep. Proced. Int. 1992, 24, 1) or Sharma and Kaur (Synthesis 1989, 9, 677) or Takai *et al* (Chem. Pharm. Bull. 1985, 33, 1116). The acid used as a catalyst may be hydrochloric acid (Klemm *et al*; J. Heterocycl. Chem. 1998, 35, 1269), or acetic acid (Reddy *et al* Indian J. Chem. Sec. B, 1988, 27, 135) or a Lewis acid such as borontrifluoride diethyl etherate. The reaction may be performed in a sealed tube, for example, using microwaves as an energy source or under vacuum. Suitable solvents for use in this reaction include halogenated hydrocarbons, e.g. dichloromethane or dichloroethane, amides, e.g. dimethylformamide, ethers such as cyclic ethers e.g. 1-4-dioxane, alcohols e.g. ethanol or esters e.g. isopropylacetate. Drying agents such as magnesium sulfate or molecular sieves may be added or the reaction may be performed using Dean Stark conditions. The reaction may be achieved at a range of temperatures e.g. from room temperature to reflux.

Carbonyl compounds of formula (vii) are either commercially available or may be prepared using methods known to those skilled in the art. Alternatively a carbonyl compound protected as an acetal may be used in the condensation reaction rather than the carbonyl compound itself. Such compounds are either commercially available or prepared using methods previously reported in the literature.

Compounds of formula (1c) may be prepared from appropriate ketones of formula (vii), e.g. 4-hydroxyproline, using standard methodology known to those skilled in the art, such as those methods as described in the examples hereinafter. For example, starting from 4-hydroxyproline of known stereochemistry, standard manipulations may afford ketones of formula (vii) as enatiomerically pure compounds. Cyclisation of these ketones with amino amides of formula (vi) may thus afford two out of four possible diastereomers of quinazolinones of formula (1c). The diastereomers thus formed may be

separated using methods known to those skilled in the art, such as by column chromatography and/or preparative HPLC.

It will be appreciated by one skilled in the art that the group R^5 in compounds of formula (vii) may be further functionalised after ring cyclisation has taken place.

Quinazolinethiones of formula (1) (where X=S) may be prepared from the corresponding quinazolinone (X=O) for example, by reaction with a thiation reagent, such as Lawesson's Reagent or P_2S_5, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, or toluene at an elevated temperature such as the reflux temperature (see for example Tetrahedron 1985, 41, 5061).

It will be appreciated that compounds of formula (1) or any preceding intermediates may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of any of formula (1) or any preceding intermediates where appropriate functional groups exist in these compounds.

For example, ester groups may be converted to the corresponding acid [-CO_2H] by acid- or base-catalysed hydrolysis depending on the nature of the ester. Acid- or base- catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol. Similarly an acid [-CO_2H] may be prepared by hydrolysis of the corresponding nitrile [-CN], using for example a base such as sodium hydroxide in a refluxing alcoholic solvent, such as ethanol.

In another example, -OH groups may be generated from the corresponding ester or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride in e.g. tetrahydrofuran or sodium borohydride in an alcohol e.g. methanol. Alternatively an alcohol may be prepared by reduction of the corresponding acid [-CO_2H], using for example lithium aluminium hydride in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon e.g. dichloromethane to yield the corresponding chloride. A base e.g. triethylamine may also be used in the reaction.

In another example, alcohol or phenol groups may be converted to ether groups groups by coupling a phenol with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate. Alternatively ether groups may be prepared by deprotonation of an alcohol, using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkylhalide.

Aldehyde or ketone groups may be obtained by oxidation of a corresponding alcohol using well known conditions. For example using an oxidising agent such as a periodinane e.g. Dess Martin, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane. An alternative oxidation may be suitably activating dimethyl sulfoxide using for example, oxalyl chloride, followed by addition of an alcohol, and subsequent quenching of the reaction by the addition of an amine base, such as triethylamine. Suitable conditions for this reaction may be using an appropriate solvent, for example, a halogenated hydrocarbon, e.g. dichloromethane at -78°C followed by subsequent warming to room temperature.

In a further example primary amine ($-NH_2$) or secondary amine (-NH-) groups may be alkylated using a reductive alkylation process employing an aldehyde or ketone and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example amine ($-CH_2NH_2$) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether, e.g. tetrahydrofuran, at a temperature from -78°C to the reflux temperature.

Compounds possessing a urea linker may be prepared by reaction of an isocyanate with an amine in the presence of a base e.g. triethylamine or DIPEA in a suitable solvent such as dichloromethane. Isocyanates may be prepared by reaction of an amine with phosgene or triphosgene in the presence of a base e.g. triethylamine in a suitable solvent such as dichloromethane.

Compounds possessing an amide linker may be prepared by reaction of an amine with an activated acid using standard methods known to those skilled in

the art. For example, acids may be activated *in situ* using for example a diimide such as EDC, advantageously in the presence of a catalyst such as a *N*-hydroxy compound, e.g. *N*-hydroxybenzotriazole, using suitable conditions, e.g. in *N,N*-dimethylformamide, prior to the subsequent addition of an amine. A base such as an amine base e.g. triethylamine or diisopropylethylamine may also be employed in the reaction. Alternative activated acids, which may be used, include acid chlorides, chloroformates or anhydrides.

Aromatic halogen substituents in the compounds may be subjected to halogen- metal exchange by treatment with a base, for example a lithium base such as *n*-butyl or *t*- butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile. Aromatic halogen substituents may also be subjected to palladium catalysed reactions, to introduce, for example, acid, ester, cyano or amino substituents.

In another example, sulfur atoms in the compounds, for example when present in a linker group L^1, L^2 or L^3 may be oxidised to the corresponding sulfoxide or sulfone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base or acid in a suitable solvent

or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol or an aqueous solvent using conventional procedures. Salts of compounds of formula (1) may be exchanged for other salts by use of conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. Where experimental detail is not given for the preparation of a reagent it is either commercially available, or it is known in the literature, for which the CAS number is quoted. ^{1}H NMR spectra were obtained at 300MHz or 400MHz unless otherwise indicated.

The following LCMS conditions were used to obtained the retention times (RT) as described herein:

LCMS conditions:

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionization

Column:	Luna C18(2) 100x4.6mm, 5µm particle size Analytical column
Column Temp:	35°C
Mobile Phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid
Flow rate:	3ml/min
Gradient:	Time (mins): % Composition B: 0 5 4.4 95 5.30 95 5.32 5 6.5 5
Run time:	6.5 mins
Typical Injection Vol:	10µl
Detector Wavelength:	DAD 200-400nm

Chiral column conditions:

Varian Gradient HPLC system consisting of Varian 9012/9050/9100 Modules and Waters fraction collector.

Column:	Chiralpak® AD 250x 20mm, 10µm particle size Prep column
Column Temp:	35°C
Mobile Phase:	A: EtOH + 0.1% DEA B: Heptane
Flow rate:	6ml/min
Isocratic:	60% A : 40% B
Run time:	18 mins
Typical Injection Vol:	320µl at 40mg/ml
Detector Wavelength:	252nm

Preparative LC conditions (Method A):

Gilson 215 liquid handler setup.

Column:	Luna C18(2) 250x21.2mm, 5µM particle size PREP column
Column Temp:	Ambient
Gradient:	Variable – depends on retention time of sample in LC-MS analysis.
Run Time:	20 mins
Flow rate:	25ml/min
Typical Injection Vol:	0.5 – 4.0ml at 25mg/ml
Detector Wavelength:	210 and 254nm
Mobile Phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid

Preparative LC conditions (Method B):

Gilson 215 liquid handler setup.

Column:	Luna C18(2) 100x21mm, 5□M particle size Prep column
Column Temp:	Ambient.
Gradient :	Variable- depends on retention of sample in LCMS screen
Run Time:	10 mins
Flow rate:	20ml/min
Typical Injection volume :	500□l
Detector Wavelength:	210 and 254nM
Mobile phase :	A: Water + 0.08% formic acid B: MeCN + 0.08 % formic acid

Retrieve medium pressure liquid chromatography (MPLC) conditions:

Column:	Redisep Isco Flash Column (4g)
Gradient:	Variable – depends on R_f of sample.
Flow rate:	Approximately 18ml/min

Abbreviations used :-

DCM – Dichloromethane; DCE – Dichloroethane;

DEA – Diethylamine; Et_2O - Diethyl ether;

DMF - *N,N*-Dimethylformamide; d_6-DMSO - Dimethyl-d_6 sulphoxide;

DIPEA - Di-*iso*-propylethylamine; EtOH – Ethanol;

EtOAc - Ethyl acetate; MeOH – Methanol;

d_4-MeOH - Methanol-d_4; TEA – Triethylamine;

PTSA - *para*-Toluenesulfonic acid

BOC – *tert*-butoxycarbonyl HOBT - 1-Hydroxybenzotriazole hydrate;

EDC - 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

HBTU - 2-[*1H*-Benzotriazole-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate

DBN - 1,8-diazobicyclo[4.3.0]non-5-ene

Intermediate 1.

2-Amino-4-methoxy-*N*-methyl-5-oxazol-5-yl-benzamide

To a solution of 2-amino-4-methoxy-5-oxazol-5-yl-benzoic acid (CAS 371251-38-6) (200mg) in dry DCM (10ml) at room temperature was added TEA

(0.33ml) and EDC (250mg) followed by methylamine hydrochloride (130mg). The reaction mixture was allowed to stir for 22 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with EtOAc to yield the title compound as a pale yellow solid (76mg, 36%). TLC R_f 0.31 (EtOAc). LCMS 248 $[M+H]^+$, RT 2.04 mins. ^1H NMR 300MHz (d_6-DMSO) 8.33 (1H, s), 8.25-8.20 (1H, m, br), 7.85 (1H, s), 7.25 (1H, s), 6.95-6.85 (2H, s, br), 6.40 (1H, s), 3.85 (3H, s), 2.75-2.70 (3H, d).

Intermediate 2.

2-Amino-4-methoxy-5-oxazol-5-yl-benzamide

2-Amino-4-methoxy-5-oxazol-5-yl-benzoic acid (CAS 371251-38-6) (3.5g), EDC (2.87g) and HOBT (2.02g) were combined in a 0.5M ammonia in dioxane solution (100ml) and stirred at room temperature for 21 hours. The reaction mixture was evaporated directly onto silica and purified by column chromatography on silica eluting with 75-100% EtOAc/heptane rising to 5% MeOH/EtOAc to give the title compound as a yellow solid (1.90g, 55%). TLC R_f 0.15 (75% EtOAc/Heptane). LCMS 234 $[M+H]^+$, RT 1.95 mins. ^1H NMR 300MHz (d_6-DMSO) 8.36 (1H, s), 7.94 (1H, s), 7.85 (1H, s, br), 7.30 (1H, s), 7.05 (3H, s, br), 6.45 (1H, s), 3.91 (3H, s).

Intermediate 3.

***tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[piperidine-4,2'-quinazoline]-1-carboxylate**

To a stirred solution of Intermediate 1 (270mg), $MgSO_4$ (500g) and PTSA (1.0mg) in DCM (10 ml) under nitrogen was added *tert*-butyl 4-oxo-1-piperdinecarboxylate (218mg). The reaction mixture was heated to 60°C for 12 hours, allowed to cool and then filtered. The filtrate was concentrated *in vacuo* and the residue dissolved in DCM (100ml) and washed with aqueous 1M aqueous HCl (30ml), aqueous Na_2CO_3 (30ml) and water (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by recrystalisation from EtOAc, Et_2O and heptane to yield the title compound as a yellow solid (386mg, 90%). TLC R_f 0.65 (EtOAc). LCMS 429 $[M+H]^+$, RT 3.20 mins. ^1H NMR 300MHz (d_6-DMSO) 8.35 (1H, s),

8.00 (1H, s), 7.33 (2H, s), 7.18 (1H, s), 6.71 (1H, s), 3.93 (3H, s), 3.93-3.83 (2H, m), 3.25-3.03 (2H, m), 2.95 (3H, s), 2.00-1.80 (4H,m) 1.42 (9H, s).

Intermediate 4.

(2-Oxo-indan-5-yl)-carbamic acid *tert*-butyl ester

5-Nitro-2-indanone (100mg), di-*tert*-butyldicarbonate (135mg), palladium on carbon (15mg), 3A powdered molecular sieves (30mg) and THF (10ml) were combined in a Parr vessel, which was purged with hydrogen gas at 100psi and heated to 50°C for 12.5 hours. The mixture was filtered through a pad of celite, washing through with THF. The solvent was removed *in vacuo* and the residue triturated with diethyl ether to yield the title compound as a mustard coloured solid (66mg, 48%).TLC R_f 0.59 (EtOAc/heptane). ^{1}H NMR 300MHz (d_6-DMSO) 9.12 (1H, s, br), 7.27 (1H, s), 7.06 (1H, d), 6.97 (1H, d), 3.3 (2H, s), 3.24 (2H, s), 1.27 (9H, s).

Intermediate 5.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'(*3'H*)-one formate salt

tert-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate (536mg) and formic acid (3ml) were combined and stirred at room temperature overnight. The mixture was concentrated carefully *in vacuo* and the resulting residue washed sparingly with DCM to afford the title compound as a solid (490mg, 72%). LCMS 315 $[M+H]^+$, RT 1.32 mins.

Intermediate 6.

Methyl 2-(2-{[(benzyloxy)carbonyl]amino}ethyl)-7-methoxy-3-methyl-6-(1,3-oxazol-5-yl)-4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylate

To a solution of Intermediate 1 (128mg) in isopropyl acetate (50ml) were added methyl 4-{[(benzyloxy)carbonyl]amino}-2-oxobutanoate (CAS 81323-56-0). (137mg) and PTSA (catalytic). The solution was stirred overnight at 95°C. The reaction mixture was evaporated directly onto silica and purified by column chromatography eluting with EtOAc to give the title compound as a tan solid (158mg, 61%). TLC R_f 0.23 (100% EtOAc). LCMS 495 $[M+H]^+$, RT 3.16 mins. ^{1}H NMR 300MHz (d_4-MeOD) 8.20 (1H, s), 8.10 (1H, s), 7.35-7.20

(6H, m), 6.40 (1H, s), 5.10 (2H, s), 4.10 (1H, s), 3.95 (3H, s), 3.65 (3H, s), 3.55-3.25 (2H, m), 3.15 (3H, s), 2.45-2.25 (2H, m).

Intermediate 7.

***iso*-Propyl-(4*R*)-4-hydroxy-D-prolinate hydrochloride**

To a suspension of *cis*-4-hydroxy-D-proline (1.0g) in dry iso-propanol (25ml) under nitrogen cooled to 0°C was added dropwise thionyl chloride (0.8ml). The reaction mixture was heated at 100°C for 6 hours. The mixture was concentrated *in vacuo* to afford the title compound as a white solid (1.6g, quantitative). ^{1}H NMR 400MHz (d_4-MeOH) 5.17-5.08 (1H, hep), 4.52-4.47 (2H, m), 3.40-3.32 (2H, m), 2.48-2.41 (1H, m), 2.36-2.32 (1H, m), 1.33-1.30 (6H, d).

Intermediate 8.

1-*tert*-Butyl 2-isopropyl-(2*R*,4*R*)-4-hydroxy-pyrrolidine-1,2-dicarboxylate

To a solution of Intermediate 7 (0.8g) in dioxane / H_2O (10ml / 10ml) cooled to 0°C was added di-*tert*-butyl dicarbonate (0.91g) followed by TEA (1.2ml) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The dioxane was removed *in vacuo* and the residue diluted with DCM / H_2O (150ml / 50ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (1.1g, quantitative). ^{1}H NMR 400MHz ($CDCl_3$) 5.11-5.04 (1H, hep), 4.36-4.23 (2H, m), 3.73-3.48 (2H, m), 3.36-3.33 (1H, d), 2.38-2.26 (1H, m), 2.09-2.02 (1H, m), 1.46 and 1.43 (9H, 2xs), 1.32-1.24 (6H, m).

Intermediate 9.

1-*tert*-Butyl 2-isopropyl-(2*R*)-4-oxopyrrolidine-1,2-dicarboxylate

To a solution of oxalyl chloride (0.53ml) in dry DCM (15ml) cooled to -78°C was added dropwise dry DMSO (0.43ml). After stirring at -78°C for 15 mins, a solution of Intermediate 8 (1.1g) in dry DCM (15ml) was added slowly and the mixture stirred at -78°C for another 40 mins. Dropwise addition of TEA (2.8ml) then took place and the reaction mixture was allowed to warm to 0°C and stirred for 60 mins. The reaction mixture was diluted with H_2O (20ml) and extracted with DCM (100ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography on silica eluting with 20% EtOAc/Heptane afforded

the title compound as a yellow oil (0.58, 53%). TLC R_f 0.76 (50% EtOAc/Hexane). ^{1}H NMR 400MHz ($CDCl_3$) 5.10-54.98 (1H, hep), 4.77-4.62 (1H, m), 3.93-3.83 (2H, m), 3.00-2.84 (1H, m), 2.57-2.50 (1H, dd), 1.46 (9H, s), 1.27-1.24 (6H, d).

Example 1.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[cyclohexane,2'-quinazolin]-4'(*3'H*)-one

To a stirred solution of 2-amino-4-methoxy-*N*-methyl-5-oxazol-5-yl-benzamide (150mg), $MgSO_4$ (500mg) and PTSA (1.0mg) in DCM (10ml) under nitrogen was added cyclohexanone (60mg). The reaction mixture was heated to 60°C for 12 hours, allowed to cool and then filtered. The filtrate was concentrated *in vacuo* and the residue taken up in DCM (100ml) and washed with aqueous 1M HCl (30ml), aqueous Na_2CO_3 (30ml), water (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by trituration with EtOAc to afford the title compound as a pale yellow solid (120mg, 60%). TLC R_f 0.48 (EtOAc). LCMS 328 $[M+H]^+$, RT 2.95 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.19 (1H, s), 8.15 (1H, s), 7.35 (1H, s), 6.67 (1H, s), 4.03 (3H, s), 3.08 (3H, s), 2.10-2.00 (2H, m), 1.95-1.82 (2H, m), 1.80-1.60 (5H, m), 1.60-1.41 (1H, m).

Examples 2-6 were prepared in a similar manner to the method of Example 1:-

Example 2.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[cyclopentane,2'-quinazolin]-4'(*3'H*)-one

From Intermediate 1 (70mg) and cyclopentanone (24mg). The residue was purified by preparative HPLC (Method A) to yield the title compound as a pale yellow solid (13mg, 15%). TLC R_f 0.36 (EtOAc). LCMS 314 $[M+H]^+$, RT 2.68 mins. ^{1}H NMR 300MHz (d_6-DMSO) 8.34 (1H, s), 7.97 (1H, s), 7.32 (1H, s), 7.24 (1H, s), 6.47 (1H, s), 3.95 (3H, s), 2.92 (3H, s), 2.12-1.99 (2H, m), 1.85-1.61 (6H, m).

Example 3.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-2,3,5,6-tetrahydro-*1'H*-spiro[pyran-4,2'-quinazolin]-4'(*3'H*)-one

From Intermediate 1 (100mg) and tetrahydro-*2H*-pyran-4-one (80mg). The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to yield the title compound as a cream solid (68mg, 51%). TLC R_f 0.48 (10%MeOH/DCM). LCMS 330 $[M+H]^+$, RT 2.30 mins. ^1H NMR 300MHz (d_6-DMSO) 8.31 (1H, s), 7.96 (1H, s), 7.30 (2H, s), 6.69 (1H, s), 3.95 (3H, s), 3.85-3.68 (4H, m), 2.98 (3H, s), 2.18-2.02 (2H,m), 1.83-1.72 (2H, m).

Example 4.

7'-Methoxy-3'-methyl-4-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[piperidine-4,2'-quinazolin]-4'(*3'H*)-one

From Intermediate 1 (100mg) and *N*-methyl-4-piperidone (0.056ml). The residue was purified by trituration with Et_2O to yield the title compound as a cream solid (60mg, 43%). TLC R_f 0.21 (10%MeOH/DCM). LCMS 343 $[M+H]^+$, RT 1.42 mins. ^1H NMR 300MHz (d_4-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.36 (1H, s), 6.65 (1H, s), 4.02 (3H, s), 3.20 (3H, s), 3.92-3.80 (2H, m), 2.54-2.35 (2H, m), 2.36 (3H, s), 2.27-2.14 (2H,m), 2.10-1.96 (2H, m).

Example 5.

3-Benzyl-7'-methoxy-3'-methyl-4-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'(*3'H*)-one

From Intermediate 1 (406mg) and 1-benzyl-3-pyrrolidinone (288mg). The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM to yield the title compound as a black solid (150mg, 23%). TLC R_f 0.6 (10%MeOH/DCM). LCMS 405.2 $[M+H]^+$, RT 1.73 mins. ^1H NMR 300MHz (d_4-MeOH) 8.23 (1H, s), 8.15 (1H, s), 7.48-7.30 (6H, m), 6.46 (1H, s), 4.02 (3H, s), 3.95-3.74 (2H, bdd), 3.27-3.16 (1H, m), 3.20 (3H, s), 3.08-2.82 (3H,m), 2.64-2.46 (1H, m), 2.32-2.18 (1H, m).

Example 6.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1,3-dihydro-*1'H*-spiro[indene-2,2'-quinazolin]-4'(*3'H*)-one

From Intermediate 1 (50mg) and 2-indanone (27mg). The residue was purified by trituration with EtOAc:Et_2O (5:1) to yield the title compound as a pale yellow solid (28mg, 38%). TLC R_f 0.7 (10%MeOH/DCM). LCMS 362 $[M+H]^+$, RT

3.31 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.24 (2H, s), 7.37 (1H, s), 7.33-7.22 (5H, m), 6.40 (1H, s), 3.98 (3H, s), 3.72 (2H, d), 3.34 (2H, d), 3.13 (3H, s).

Example 7.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4,5-dihydro-*1'H*-spiro[furan-3,2'-quinazolin]-4'(*3'H*)-one

To a stirred solution of Intermediate 1 (50mg), $MgSO_4$ (0.5g) and PTSA (1.0mg) in DCE (10ml) under nitrogen was added dihydrofuran-3-one (CAS 22929-52-8) (80mg). The reaction mixture was heated to 91°C for 8 hours and allowed to cool. The reaction mixture was taken up in EtOAc (100ml) and washed with aqueous $NaHCO_3$ (20ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was taken up in DCM (5ml), filtered and the filtrate concentrated *in vacuo* and purified by trituration with MeOH:Et_2O (1:20) to afford the title compound as a solid (8mg, 13%). TLC R_f 0.45 (EtOAc). LCMS 316 $[M+H]^+$, RT 2.26 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.25 (1H, s), 8.20 (1H, s), 7.40 (1H,s), 6.50 (1H,s), 4.17 (1H,d), 4.13-3.95 (2H,m), 4.03 (3H,s), 3.73 (1H,d), 3.15 (3H,s), 2.65-2.55 (1H,m), 2.35-2.22 (1H,m).

Example 8.

***tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirred solution of Intermediate 1 (800mg) in DCE (20 ml) under nitrogen was added 1-*N*-Boc-3-pyrrolidinone (600mg). The reaction mixture was heated to 91°C for 14 hours and allowed to cool. The reaction mixture was taken up in EtOAc (100ml) and washed with aqueous Na_2CO_3 (40ml) and aqueous 1M HCl (40ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a brown solid (1.15 g, 86%). TLC R_f 0.48 (EtOAc). LCMS 415 $[M+H]^+$, RT 3.05 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.19 (1H, s), 8.18 (1H, s), 7.37 (1H,s), 6.50 (1H,s), 4.00 (3H,s), 3.72-3.58 (4H,m), 3.12 (3H,s), 2.75-2.55 (1H,m), 2.32-2.12 (1H,m), 1.52 and 1.47 (9H, 2xd).

Example 8a.

Enantiomer 1 of *tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

Example 8 (80mg) was separated into its component enantiomers on a chiral pak column eluting with 3:1 A:B (A = EtOH + 10.1% DEA) (B=Heptane). This gave enantiomer 1 as a solid (32 mg, 80%). Chiral LC RT 5.89 mins. LCMS 415 $[M+H]^+$, RT 3.05 mins.

Example 8b.

Enantiomer 2 of *tert*-Butyl-7'-methoxy-3'-methyl-6'-(1,3oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

Example 8 (80mg) was separated into its component enantiomers on a chiral pak column eluting with 3:1 A:B (A = EtOH + 10.1% DEA) (B=Heptane). This gave enantiomer 2 as a solid (34 mg, 85%). Chiral LC RT 7.14 mins. LCMS 415 $[M+H]^+$, RT 3.05 mins.

Example 9.

***tert*-Butyl 7'-methoxy-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirred solution of Intermediate 2 (360mg) in DCE (20 ml) under nitrogen was added 1-*N*-Boc-3-pyrrolidinone (286mg). The reaction mixture was heated to 80°C for 3.5 hours and allowed to cool. The reaction mixture was taken up in EtOAc (100ml) and washed with aqueous Na_2CO_3 (30ml) and aqueous 1M HCl (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound (579mg, 94%). TLC R_f 0.22 (5%MeOH/DCM). LCMS 401 $[M+H]^+$, RT 3.25 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.18 (1H, s), 7.37 (1H, s), 6.48 (1H, s) 4.00 (3H, s), 3.58 (2H, m), 3.55 (2H, m), 2.25 (2H, m), 1.50 (9H, 2xs).

Example 10.

***tert*-Butyl [7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1,3,3',4'-tetrahydro-*1'H*-spiro[indene-2,2'-quinazolin]-5-yl]carbamate**

To a stirred solution of Intermediate 1 (23mg) in DCE (4 ml) under nitrogen was added Intermediate 4 (66mg). The reaction mixture was heated at reflux for 18 hours and allowed to cool. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 70% EtOAc/heptane. The product was further purified by trituration with DCM/pentane to yield the title compound as a sandy coloured solid (14mg, 33%). TLC R_f 0.59 (EtOAc). LCMS 477 $[M+H]^+$, RT 3.60 mins. ^1H NMR

300MHz (d_6-DMSO) 9.30 (1H, s, br), 8.34 (1H, s), 8.00 (1H, s), 7.5 (1H, s), 7.4 (1H,s), 7.3 (1H, s), 7.2 (1H, d), 7.1 (1H, d), 6.4 (1H, s), 3.85 (3H, s), 3.5 (2H, m), 3.1 (2H, m), 2.85 (3H, s), 1.45 (9H, s).

Example 11.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-2,3-dihydro-*1'H*-spiro[indene-1,2'-quinazolin]-4'(*3'H*)-one

To a stirred solution of Intermediate 1 (50mg) and PTSA (1.0mg) in DMF (2 ml), was added 1-indanone (80mg). The reaction mixture was heated to 170°C for 30 mins in a microwave reactor and allowed to cool. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative HPLC (Method A) to afford the title compound as a solid (27.8mg, 38%). HPLC: RT 3.20 mins. LCMS: 362 $[M+H]^+$, RT 3.25 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.23 (1H, s), 8.08 (1H, s), 7.50-7.45 (1H,d), 7.35-7.25 (4H,m), 6.33 (1H,s), 3.95 (3H, s), 3.09-3.02 (2H,m), 2.76 (3H,s), 2.00-2.45 (2H,m).

Example 12.

7'-Methoxy-3'-methyl-5-nitro-6'-(1,3-oxazol-5-yl)-1,3-dihydro-*1'H*-spiro[indene-2,2'-quinazolin]-4'(*3'H*)-one

To a stirred solution of Intermediate 1 (200mg) and PTSA (1.0mg) in DMF (5 ml) was added 5-nitro-2-indanone (430mg). The reaction mixture was heated to 110°C for 30 mins in a microwave reactor and allowed to cool. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 70% EtOAc/heptane followed by 5% MeOH/DCM to afford the title compound as a brown solid (252mg, 77%). TLC R_f 0.68 (EtOAc). LCMS 407 $[M+H]^+$, RT 3.15 mins. ^{1}H NMR 300MHz (d_6-DMSO) 8.55 (1H, s), 8.17 (1H, s), 8.15 (1H, dd), 8.05 (1H, s), 7.65 (1H, s), 7.55 (1H,d), 7.35 (1H, s), 6.37 (1H,s), 3.9 (3H, s), 3.8 (1H, d), 3.7 (1H,d), 3.35 (1H,d), 3.27 (1H,d), 2.95 (3H,s).

Example 13.

5-Amino-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1,3-dihydro-*1'H*-spiro[indene-2,2'-quinazolin]-4'(*3'H*)-one

Example 12 (246mg) and palladium on carbon were combined in EtOH (15ml) and stirred under hydrogen gas for 48 hours. The reaction mixture was filtered through a pad of celite and the filtrate concentrated *in vacuo*. The resulting residue was dissolved in DCM (30ml) and washed with aqueous 1M

HCl (2x15ml). The aqueous layers were collected and extracted with DCM (3x30ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting residue was purified by column chromatography on silica eluting with 50-100% EtOAc/heptane to yield the title compound as a yellow solid (12.9 mg, 56%). TLC R_f 0.42 (EtOAc). LCMS: 377 $[M+H]^+$, RT 1.78 mins. ^1H NMR 300MHz (d_4-MeOH) 8.23 (1H, s), 8.23 (1H, s), 7.37 (1H, s), 7.00 (1H, d), 6.70 (1H, s), 6.65 (1H, d), 6.43, 4.00 (3H, s), 3.57 (2H, m), 3.23 (2H, m), 3.05 (3H, s).

Examples 14-15 were prepared in a similar manner to the method of example 12:-

Example 14.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4,6-dihydro-*1'H*-spiro[cyclopenta[b]thiophen-5,2'-quinazolin]-4'(*3'H*)-one

From Intermediate 1 (100mg) and 4,6-dihydrocyclopenta[*b*]thiophen-5-one (CAS 33449-51-3) (270mg). The residue was purified by column chromatography on silica eluting with 75% EtOAc/heptane followed by trituration with DCM/Et_2O to yield the title compound as an off-white solid (34mg, 23%).R_f 0.62 (EtOAc). LCMS 368 $[M+H]^+$, RT 3.14 mins. ^1H NMR 300MHz (d_6-DMSO) 8.35 (1H, s), 8.0 (1H, s), 7.8 (1H,s), 7.48 (1H, d), 7.32 (1H, s), 6.95 (1H, d), 6.4 (1H, s), 3.9 (3H, s), 3.5 (2H, m), 3.1 (2H,m), 2.9 (3H, s).

Example 15.

7-Methoxy-3-methyl-6-(1,3-oxazol-5-yl)-4',5'-dihydro-*1'H*-spiro[quinazoline-2,3'-thiophen]-4(*3'H*)-one

From Intermediate 1 (200mg) and tetrahydrothiophen-3-one (0.37ml). The residue was purified by column chromatography on silica eluting with 75-100% EtOAc/heptane followed by trituration with DCM/Et_2O to yield the title compound as an off-white solid (200mg, 78%). TLC R_f 0.38 (EtOAc). LCMS 332 $[M+H]^+$, RT 2.74 mins. ^1H NMR 300MHz (d_6-DMSO) 8.35 (1H, s), 8.0 (1H, s), 7.38 (1H, s), 7.29 (1H, s), 6.62 (1H, s), 3.95 (3H, s), 3.15 (1H, d), 3.1 (1H,m), 3.05 (3H, s), 2.95 (1H, m), 2.85 (1H, d), 2.45 (1H, m), 2.2 (1H, m).

Example 16.

(*3R*)-7'-Methoxy-3,3'-dimethyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[cyclopentane-1,2'-quinazolin]-4'*(3'H)*-one

To a stirred solution of Intermediate 1 (100mg) and PTSA (1.0mg) in DMF (3ml) was added (*R*)-(+)-3-methyl cyclopentanone (0.1ml). The reaction mixture was heated to 150°C for 30 mins in a microwave reactor and allowed to cool. The solvent was removed *in vacuo* and the residue purified by preparative HPLC (Method A) to afford the title compound as a beige solid (13mg, 10%). LCMS 328 $[M+H]^+$, RT 3.10 mins. ^1H NMR 300MHz (d_6-DMSO) 8.3 (1H, s), 7.9 (1H, s), 7.3 (1H, s), 7.25 (1H, s), 6.4 (1H, s), 3.9 (3H, s), 2.9 (3H, s), 2.4-2.25 (1H, m), 2.2-1.7 (4H, m), 1.5-1.2 (2H, m), 1.0 (3H, m).

Example 17.

Ethyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[cyclopentane-1,2'-quinazoline]-3-carboxylate

Intermediate 1 (123mg), acetic acid (10ml) and ethyl 3-oxocyclopentane-1-carboxylate (135mg) were combined and heated to 70°C under a slight vacuum for 2 hours. After cooling to room temperature the solvent was removed *in vacuo* and the residue purified by column chromatography on silica to afford the title compound as an off-white solid (154mg, 81%). TLC R_f 0.525 (20% EtOH / EtOAc). LCMS 386 $[M+H]^+$, RT 2.95 mins. ^1H NMR 300MHz (d_6-DMSO) 8.35 (1H, s), 7.95 (1H, 2 x s), 7.35 (2H, s), 6.45 (1H, d), 4.1 (2H, m), 3.9 (3H, 2 x s), 3.1-2.9 (4H, m), 2.4-1.8 (4H, m), 1.4-1.1 (5H, m).

Example 18.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[cyclopentane-1,2'-quinazoline]-3-carboxylic acid

Example 17 (145mg), $LiOH.H_2O$ (24mg), THF (5ml) and H_2O (1ml) were combined and stirred at room temperature for 18 hours. The solvents were removed *in vacuo* and the residue partitioned between 1M HCl (20ml) and EtOAc (20ml). The EtOAc layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a yellow solid (112mg, 84%). LCMS 358 $[M+H]^+$, RT 2.24 mins. ^1H NMR 300MHz (d_6-DMSO) 12.3 (1H, br s), 8.3 (1H, s), 7.95 (1H, 2 x s), 7.3 (2H, m), 6.4 (1H, d), 3.9 (3H, 2 x s), 3.0-2.8 (4H, m), 2.35-1.75 (6H, m).

Example 19.

7-Methoxy-3-methyl-6-(1,3-oxazol-5-yl)-4',5'-dihydro-*1'H*-spiro[quinazoline-2,3'-thiophen]-4(*3'H*)-one-1',1'-dioxide

To a solution of Example 15 in methanol (10ml) was added a solution of oxone® in H_2O (5ml) and the reaction mixture stirred at room temperature for 18 hours. The solvent was removed *in vacuo*. The residue was purified by triturating with H_2O and washing with Et_2O followed by further trituration with MeOH/DCM to yield the title compound as an off-white solid (26mg, 24%). LCMS 364 $[M+H]^+$, RT 2.22 mins. ^1H NMR 300MHz (d_6-DMSO) 8.3 (1H, s), 8.0 (1H, s), 7.8 (1H, s), 7.35 (1H, s), 6.47 (1H, s), 3.92 (3H, s), 3,4 (4H, m), 3.0 (3H, s), 2.75 (1H, m), 2.55 (1H, m).

Example 20.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[piperidine-4,2'-quinazolin]-4'(*3'H*)-one

Formic acid (3ml) and Intermediate 3 (0.25g) were stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and taken up in aqueous 1M HCl (25ml) and washed with Et_2O (50ml). The aqueous solution was basified with aqueous 1M NaOH and extracted with EtOAc (50ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a white solid (130mg, 68%). LCMS 329 $[M+H]^+$, RT 1.35 mins. ^1H NMR 300MHz (d_6-DMSO) 8.32 (1H, s), 7.96 (1H, s), 7.30 (1H, s), 7.11 (1H, s), 7.74 (1H, s), 3.90 (3H, s), 2.95 (3H, s), 2.86-2.77 (4H, m), 1.93-1.68 (4H, m).

Example 21.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'(*3'H*)-one dihydrochloride salt

Example 8 (0.20g), DCM (10ml) and HCl (2M in Et_2O, 30ml) were stirred at room temperature for 1 hour. The reaction mixture was filtered and the solid dried *in vacuo* to yield the title compound as a solid (206mg, quantitative). TLC R_f 0.13 (10% MeOH/DCM). LCMS 315 $[M+H]^+$, RT 1.33 mins. ^1H NMR 300MHz (d_4-MeOH) 8.36 (1H, s), 8.25 (1H, s), 7.47 (1H, s), 6.61 (1H, s), 4.06 (3H, s), 3.77-3.65 (2H, m), 3.57 (2H, 2xd), 3.17 (3H, s), 2.90-2.70 (1H,m), 2.52-2.40 (1H, m).

Examples 21a – 22 were prepared in a similar manner to the method of Example 21:-

Example 21a.

7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one hydrochloride

From enantiomer 1 of Example 8 (60mg) and HCl (2M in Et_2O, 20ml) to yield the title compound as a solid (50mg, 86%). TLC R_f 0.10 (10% MeOH/DCM). LCMS 315 $[M+H]^+$, RT 1.48 mins.

Example 22.

7'-methoxy-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one hydrochloride

From Example 9 (519mg) and HCl (2M in Et_2O, 20ml) to yield the title compound as a solid (494 mg, quantitative yield). TLC R_f 0.072 (10% MeOH/DCM). LCMS 301 $[M+H]^+$, RT 1.36 mins. ^1H NMR 300MHz (d_4-MeOH) 8.48 (1H, s), 8.25 (1H, s), 7.52 (1H, s), 6.57 (1H, s), 4.06, (3H,s), 3.68 (2H, m), 3.55 (2H,m), 2.48 (2H, t).

Example 23.

(*3S*)-Tetrahydrofuran-3-yl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[piperidine-4,2'-quinazoline]-1-carboxylate

A solution of Example 20 (50mg), (3*S*)-tetrahydrofuranylsuccinimidyl-carbonate (CAS 138499-08-8) (35mg) and TEA (0.021ml) in DCM (5ml) and DMF (5ml) were stirred at room temperature under nitrogen for 2 hours. The solvent was removed *in vacuo* and the reaction mixture was taken up in DCM (100ml) and washed with 1M HCl (40ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to yield the title compound as a cream solid (36mg, 54%). TLC R_f 0.43 (10% MeOH/DCM). LCMS 443 $[M+H]^+$, RT 2.48 mins. ^1H NMR 300MHz (d_4-MeOH) 8.23 (1H, s), 8.22 (1H, s), 7.39 (1H, s), 6.66 (1H, s), 5.31-5.24 (1H, m), 4.24-4.12 (2H, m), 4.04 (3H, s), 4.01-3.84 (4H, m), 3.34-3.12 (2H, m), 3.14 (3H, s), 2.32-2.11 (6H,m).

Example 24 was prepared in a similar manner to the method of Example 23:-

Example 24.

(*3S*)-Tetrahydrofuran-3-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

From Example 21 (50mg), (3*S*)-tetrahydrofuranylsuccinimidyl-carbonate (CAS 138499-08-8) (33mg) and TEA (0.1ml) in DCM (5ml) and DMF (10ml). Purification by column chromatography on silica eluting with 5-10% MeOH/DCM afforded the title compound as a beige solid (17mg, 28%). LCMS 429 $[M+H]^+$, RT 2.39 mins. ^1H NMR 400MHz (d_6-DMSO) 8.33 (1H, s), 8.00 (1H,s), 7.53 (1H, d), 7.32 (1H, s), 6.5 (1H, s), 5.12 (1H, m), 3.92 (3H, s), 3.8-3.42 (8H, m), 3.00 (3H, s), 2.09 (3H, m), 1.9 (1H, m).

Example 25.

1-Benzoyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

To a stirred solution of benzoic acid (17.4mg), HBTU (54mg) and DIPEA (0.076ml) in DMF (10ml) was added, after 5 mins, Example 21 (50mg). The mixture was stirred under nitrogen for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (100ml) and washed with aqueous Na_2CO_3 (30ml) and aqueous 1M HCl (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM gradient to yield the title compound as a solid (32mg, 53%). TLC R_f 0.13 (EtOAc). LCMS 419 $[M+H]^+$, RT 2.57 mins. ^1H NMR 300MHz (d_4.MeOH) 8.27 and 8.26 (1H,2xs), 8.23 and 8.16 (1H, 2xs), 7.67-7.45 (5H, s), 7.43 and 7.40 (1H, 2xs), 6.59 and 6.53 (1H, 2xs), 4.05 and 4.00 (3H, 2xs), 4.05-3.67 (3H, m), 3.62 (1H,d), 3.25 and 3.21 (3H, 2xs), 2.95-2.65 (1H, m), 2.40-2.25 (1H, m).

Examples 26 - 42 were prepared in a similar manner to the method of Example 25:-

Example 26.

1-(3-Furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3H')*-one

From Example 21 (50mg) and 3-furoic acid (16mg) The residue was purified by trituration with MeOH:EtOAc:Et_2O (1:3:10) to yield the title compound as a solid (24mg, 45%). TLC R_f 0.49 (10% MeOH/DCM). LCMS 409 $[M+H]^+$, RT 2.39 mins. ^1H NMR 300MHz (d_4-MeOH) 8.26 (1H, s), 8.25 (1H, s), 8.17 and 8.07 (1H, 2xs), 7.67 and 7.60 (1H, 2xs), 7.40 (1H, d), 6.89 and 6.79 (1H, 2xs), 6.53 (1H, d), 4.13-3.89 (7H, m), 3.23 (3H, s), 2.87-2.73 (1H, m), 2.45-2.38 (1H, m).

Example 27.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(phenylacetyl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and phenyl acetic acid (19mg) The residue was purified by trituration with MeOH:EtOAc:Et_2O to yield the title compound as a solid (8mg, 13%). TLC R_f 0.46 (5% MeOH/DCM). LCMS 433 $[M+H]^+$, RT 2.65 mins. ^1H NMR 300MHz (d_4-MeOH) 8.36 and 8.32 (s), (1H, 2xs), 8.35 and 8.34 (1H, 2xs), 7.56-7.27 (6H, m), 6.62 and 6.43 (1H, 2xs), 4.15 and 4.12 (3H, 2xs), 4.03-3.76 (6H, m), 3.24 (3H, s), 2.92-2.79 (1H, m), 2.50-2.30 (1H, m).

Example 28.

7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(tetrahydro-*2H*-pyran-4-ylcarbonyl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and tetrahydropyran-4-carboxylic acid (19mg). The residue was purified by column chromatography on silica eluting with 4-7% MeOH/DCM to yield the title compound as a solid (35mg, 57%). TLC R_f 0.46 (10% MeOH/DCM). LCMS 427 $[M+H]^+$, RT 2.21 mins. ^1H NMR 300MHz (d_4-MeOH) 8.37-8.35 (2H, m), 7.52 (1H, s), 6.66 and 6.60 (1H, 2xs), 4.20-3.80 (7H, m), 3.70-3.50 (4H, m), 3.29 and 3.25 (3H, 2xs), 2.92-2.76 (2H, m), 2.50-2.31 (1H, m), 2.00-1.73 (4H, m).

Example 29.

1-Isonicotinoyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and isonicotinic acid (18mg). The aqueous phases were re-extracted with DCM (3x50ml) after first basifying the acidic layer. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting

with 6-10% MeOH/DCM to yield the title compound as a solid (35mg, 58%). TLC R_f 0.54 (10% MeOH/DCM). LCMS 420 $[M+H]^+$, RT 1.91 mins. ^1H NMR 300MHz (d_4-MeOH) 8.89-8.86 and 8.78-8.76 (2H, 2xm), 8.39 and 8.37 (1H, 2xs), 8.34 and 8.30 (1H, 2xs), 7.79-7.76 and 7.69-7.66 (2H, 2xm), 7.54 and 7.51 (1H, 2xs), 6.67 and 6.65 (1H, 2xs), 4.17 and 4.14 (3H, 2xs), 4.17-3.66 (4H, m), 3.36 and 3.32 (3H, 2xs), 3.00-2.78 (1H, m), 2.55-2.34 (1H, m).

Example 30.

1-(3-Aminobenzoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (100mg) and 3-aminobenzoic acid (35mg). Note: no acidic wash. The residue was purified using an MPLC Retrieve eluting with 0-5% MeOH/DCM followed by dissolving in DCM (30ml) and washing with dilute citric acid (20ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a solid (83mg, 72%). TLC R_f 0.66 (10% MeOH/DCM). LCMS 434 $[M+H]^+$, RT 2.02 mins. ^1H NMR 300MHz (d_6-DMSO) 8.36 and 8.34 (1H, 2xs), 8.04 and 7.96 (1H, 2xs), 7.67 and 7.53 (1H, 2xs), 7.36 and 7.33 (1H, 2xs), 7.13-7.06 and 7.03-6.98 (1H, 2xtr), 6.76-6.54 (3H, m), 6.52 (1H, s), 5.36-5.14 (2H, s, br), 3.96 and 3.93 (3H, 2xs), 3.90-3.38 (4H, m), 3.33 (3H, s), 2.72-2.55 (1H, m), 2.22-2.03 (1H, m).

Example 31.

7'-Methoxy-3'-methyl-1-(morpholin-4-ylacetyl)-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and *N*-morpholino acetic acid (19mg). Note: no acidic wash. The residue was purified using an MPLC Retrieve eluting with 3-5% MeOH/DCM to yield the title compound as a solid (17mg, 30%). TLC R_f 0.43 (10% MeOH/DCM). LCMS 442 $[M+H]^+$, RT 1.47 mins. ^1H NMR 300MHz (d_6-DMSO) 8.34 (1H, s), 8.00 (1H, s), 7.49 and 7.45 (1H, 2xs), 7.33 (1H, s), 6.51 and 6.44 (1H, 2xs), 3.91 (3H, s), 3.87-2.92 (10H, m), 3.00 and 2.98 (3H, 2xs), 2.61-2.24 (5H, m), 2.17-1.97 (1H, m).

Example 32.

***tert*-Butyl (3-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}benzyl)carbamate**

From Example 21 (100mg) and Boc-(3-aminomethyl)-benzoic acid (65mg). The residue was purified using an MPLC Retrieve eluting with 0-5% MeOH/DCM to yield the title compound as a solid (115mg, 81%). TLC R_f 0.66 (10% MeOH/DCM). LCMS 548 $[M+H]^+$, RT 2.92 mins. ^1H NMR 300MHz (d_6-DMSO) 8.34 and 8.30 (1H, 2xs), 8.01 and 7.92 (1H, 2xs), 7.66 and 7.52 (1H, 2xs), 7.48-7.20 (6H, m), 4.20-3.43 (9H, m), 3.00 (3H, s), 2.73-2.50 (1H, m), 2.17-2.00 (1H, m) 1.37 and 1.34 (9H, 2xs).

Example 33.

1-(2-Furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 2-furoic acid (15mg). The residue was purified using an MPLC Retrieve eluting with 5% MeOH/DCM to yield the title compound as a solid (23mg, 43%). TLC R_f 0.51 (10% MeOH/DCM). LCMS 409 $[M+H]^+$, RT 2.37 mins. ^1H NMR 300MHz (d_6-DMSO) 8.33 (1H, s), 8.01 (1H, s), 7.97 and 7.81 (1H, 2xs), 7.58 (1H, s), 7.33 (1H, s), 7.18-7.11 (1H, m), 6.70-6.59 (1H, m), 6.49 (1H, s), 4.10-3.97 (2H, m), 3.97 (3H, s), 3.83-3.68 (2H, m), 3.02 (3H, s), 2.71-2.53 (1H, m), 2.24-2.02 (1H, m).

Example 33a.

1-(2-Furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21a (120mg) and 2-furoic acid (36mg). The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to yield the title compound as a solid (35mg, 26%). TLC R_f 0.2 (5% MeOH/DCM). LCMS 409 $[M+H]^+$, RT 2.42 mins. ^1H NMR 300MHz (d_4-MeOD) 8.20 (2H, s), 7.80 (1H, s), 7.70 (1H, s), 7.40 (1H, s), 7.30-7.15 (1H, m), 6.75-6.55 (1H, m), 6.50 (1H, s), 4.30-4.15 (2H, m), 4.00-3.85 (5H, m), 3.20 (2H, s), 2.90-2.70 (1H, m), 2.45-2.25 (1H, m).

Example 34.

7'-Methoxy-3'-methyl-1-[(1-methyl-*1H*-pyrrol-2-yl)carbonyl]-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and *N*-methylpyrrole-2-carboxylic acid (16mg). The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (7mg, 13%). LCMS 422 $[M+H]^+$, RT 2.58 mins. ^1H NMR 300MHz (d_6-DMSO) 8.32 (1H, s), 8.00 (1H, s), 7.55 (1H, s), 7.33 (1H, s),

6.94 (1H, s), 6.55 (1H, s, br), 6.50 (1H, s), 6.05 (1H, s, br), 3.95-3.85 (5H, m), 3.80-3.70 (5H, s), 3.07 (3H, s), 2.70-2.60 (1H, m), 2.20-2.10 (1H, m).

Example 35.

7'-Methoxy-3'-methyl-1-[(1-methyl-*1H*-imidazol-2-yl)carbonyl]-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 1-methyl-*1H*-imidazole-2-carboxylic acid (49mg) The residue was purified by column chromatography on silica eluting with 5%MeOH/DCM to yield the title compound as an off-white solid (35.9mg, 66%). TLC R_f 0.08 (5% MeOH/DCM). LCMS 423 $[M+H]^+$, RT 2.14 mins. ^1H NMR 300MHz (d_6-DMSO) 8.30 (1H, s), 7.99 (1H, d), 7.52 and 7.32 (1H, 2xs), 7.28 (1H, s), 7.02 and 6.92 (1H, 2xs), 6.45 (1H, d), 4.25 (2H, m), 3.91 (3H, s), 3.88 (3H, s), 3.80-3.70 (2H, m), 3.00 (3H, s), 2.63-2.52 (1H, m), 2.18-2.04 (1H, m).

Example 36.

1-(1-Benzothien-3-ylcarbonyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 1-benzothiophene-3-carboxylic acid (23mg). The residue was dissolved in DCM (10ml) and washed with water (3x10ml). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a residue that was purified by column chromatography on silica eluting with 4%MeOH/DCM to yield the title compound as a solid (16mg, 26%). TLC R_f 0.19 (5% MeOH/DCM). LCMS 475 $[M+H]^+$, RT 2.97 mins. ^1H NMR 300MHz (d_6-DMSO, 90°C) 8.21 (1H, s), 8.08-7.98 (4H, m), 7.45-7.40 (3H, m), 7.30 (1H, m), 6.54 (1H, s), 3.96 (3H, s), 3.95-3.71 (4H, m), 3.05 (3H, s), 2.72-2.63 (1H, m), 2.29-2.20 (1H, m).

Example 37.

7'-methoxy-3'-methyl-1-(2-methyl-2-phenylpropanoyl) -6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and α,α-dimethyl phenyl acetic acid (64mg). The residue was diluted with water (10ml) and extracted with EtOAc (3x10ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (13.8mg, 23%). TLC R_f 0.13

(5% MeOH/DCM). LCMS 461 $[M+H]^+$, RT 2.95 mins. ^1H NMR 300MHz (d_4-MeOH) 8.16 (1H, s), 7.92 (1H, s), 7.34 (1H, s), 7.10-7.03 (4H, m), 6.90-6.83 (1H, m), 6.18 (1H, s), 3.99 (3H, s), 3.80-3.75 (2H, m), 3.32-3.22 (2H, m), 3.10 (3H, s), 3.80-3.70 (1H, m), 2.25-2.15 (1H, m), 1.70 (3H, s), 1.53 (3H, s).

Example 38.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-{5-[4-(trifluoromethyl)phenyl]-2-furoyl}-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From 5-[3-(trifluoromethyl) phenyl]-2-furoic acid (82mg), HBTU (121mg) and DIPEA (0.11ml) in DMF (20ml) and Example 21 (112mg). Purification by column chromatography on silica eluting with 3-5% MeOH/DCM afforded the title compound as a solid (110mg, 62%). TLC R_f 0.28 (5%MeOH/DCM). LCMS 553 $[M+H]^+$, RT 3.49 mins. ^1H NMR 300MHz (d_4-MeOH) 8.25 (1H, s), 8.22 (1H, s), 8.15 (1H, m), 8.02 and 7.9 (1H, s and d), 7.72-7.6 (2H, m), 7.4 and 7.29 (1H, s and d), 7.38 (1H, s), 7.21 and 7.10 (1H, d), 6.55 (1H, s), 4.4-3.9 (7H, m), 3.29 and 3.25 (3H, 2xs), 2.85 (1H, m), 2.40 (1H, m).

Example 39.

***N*-[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1,3,3',4'-tetrahydro-*1'H*-spiro[indene-2,2'-quinazolin]-5-yl]acetamide**

From acetic acid (0.007ml), HBTU (49mg) and DIPEA (0.05ml) in DMF (5ml) and Example 13 (50mg). The residue was triturated in DCM/pentane to yield the title compound as a yellow solid (14.3 mg, 26%). TLC R_f 0.32 (10%MeOH/DCM). LCMS 419 $[M+H]^+$, RT 2.58 mins. ^1H NMR 300MHz (d_4-MeOH) 8.19 (1H, s), 8.18 (1H,s), 7.52 (1H, s), 7.22 (1H, s), 7.31 (1H, m), 7.18 (1H, d), 6.37 (1H, s), 3.95 (3H, s), 3.62 (2H, dd), 3.30 (2H, dd), 3.05 (3H, s), 2.12 (3H, s).

Example 40.

***N*-[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1,3,3',4'-tetrahydro-*1'H*-spiro[indene-2,2'-quinazolin]-5-yl]-3-furamide**

From 3-furoic acid (9mg), HBTU (30mg) and DIPEA (0.03ml) in DMF (3ml) and Example 13 (50mg)). The residue was triturated in DCM/pentane to yield the title compound as a white solid (12.9 mg, 34%). TLC R_f 0.51 (10%MeOH/DCM). LCMS 471 $[M+H]^+$, RT 3.02 mins. ^1H NMR 300MHz (d_4-MeOH) 8.25 (1H, s), 8.23 (1H, s), 7.65 (1H, s), 7.50 (1H, dd), 7.39 (1H, s),

7.27 (1H, d), 6.97 (1H, dd), 6.43 (1H, s), 4.00 (3H, s), 3.70 (2H, dd), 3.35 (2H, dd), 3.10 (3H, s).

Example 41.

***N*-(2,2-dimethylpropyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[cyclopentane-1,2'-quinazoline]-3-carboxamide**

From Example 18 (18mg), HBTU (38mg) and TEA (2 drops) in DMF (1ml) and neopentylamine (2 drops). Purification by preparative HPLC (Method A) afforded the title compound (5mg, 23%). LCMS: 427 $[M+H]^+$, RT 2.92 mins. ^1H NMR 400MHz (d_4-MeOH) 8.32 (1H, s), 8.17 (1H, s), 8.14 (1H, s), 7.91-7.86 (1H, tr), 7.30 (1H, s), 6.40 (1H, s), 3.97 (3H, s), 3.15 (3H, s), 3.04-2.90 (3H, m), 2.5-2.4 (1H, m), 2.23-2.20 (2H, d), 2.15-2.05 (1H, m), 2.00-1.88 (2H, m), 0.93 (9H, s).

Example 42.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-3-(pyrrolidin-1-ylcarbonyl)-*1'H*-spiro[cyclopentane-1,2'-quinazolin]-4'*(3'H)*-one

From Example 18 (73mg), HBTU (76mg) and TEA (0.055µl) in DMF (3ml) and pyrrolidine (0.034ml). Purification by preparative HPLC (Method A) afforded the title compound as a single diastereomer (18mg, 22%). LCMS: 411 $[M+H]^+$, RT 2.50 mins. ^1H NMR 400MHz (d_4-MeOH) 8.20 (1H, s), 8.17 (1H, s), 7.35 (1H, s), 6.45 (1H, s), 4.00 (3H, s), 3.60 (2H, m), 3.45 (2H, m), 3.27 (1H, m), 3.15 (3H, s), 2.40 (2H, m), 2.20 (2H, m), 1.95 (6H, m).

Example 43.

1-[3-(Aminomethyl)benzoyl]-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one dihydrochloride

Example 32 (53mg), DCM (3ml) and HCl (2M in Et_2O, 10ml) were stirred at room temperature for 5 minutes. The reaction mixture was concentrated carefully *in vacuo* at 40°C to yield the title compound as a solid (58mg, quantitative). TLC R_f 0.05 (10% MeOH/DCM). LCMS 448 $[M+H]^+$, RT 1.57 mins. ^1H NMR 300MHz (d_6-DMSO) 8.37 and 8.34 (1H, 2xs), 8.00 and 7.94 (1H, 2xs), 7.75-7.43 (5H, m), 7.36 and 7.31 (1H, 2xs), 6.57 and 6.50 (1H, 2xs), 4.10 and 4.04 (2H, 2xs), 3.95 and 3.90 (3H, 2xs), 3.95-3.50 (4H, m), 3.05 (3H, s), 2.76-2.58 (1H, m), 2.22-2.04 (1H, m).

Example 44.

1-(2,2-Dimethylpropanoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

Intermediate 5 (100mg), DCM (10ml), DMF (2ml) and DIPEA (1ml) were stirred at room temperature under nitrogen for 5 mins. To the reaction mixture was added trimethyl acetyl chloride (0.03ml) and the mixture was stirred for 30 mins. The reaction was concentrated *in vacuo*, taken up in EtOAc (100ml) and washed with aqueous Na_2CO_3 (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 4% MeOH /DCM to yield the title compound as a solid (4.6mg, 4.5%). TLC R_f 0.56 (10% MeOH/DCM). LCMS 399 $[M+H]^+$, RT 2.59 mins. ^1H NMR 300MHz (d_4-MeOH) 8.25 (2H, s), 8.40 (1H, s), 6.55 (1H, s), 4.03 (3H, s), 4.02-3.80 (4H, m), 3.21 (3H, s), 2.80-2.65 (1H, m), 2.29-2.21 (1H, m).

Examples 45-46 were prepared in a similar manner to the method of Example 44:-

Example 45.

***N*-Ethyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylic acid methylamide**

From Example 21 (100mg) and ethyl isocyanate (0.019ml). The residue was purified by trituration with MeOH:Et_2O (1:20). The filtrate was concentrated *in vacuo* to yield the title compound as a solid (20mg, 20%). TLC R_f 0.07 (5% MeOH/DCM). LCMS 386 $[M+H]^+$, RT 2.12 mins. ^1H NMR 300MHz (d_4-MeOH) 8.35 (1H, s), 8.23 (1H, s), 7.43 (1H, s), 6.52 (1H, s), 4.00 (3H, s), 3.70-3.61 (4H, m), 3.33 (2H, q), 3.16 (3H, s), 2.76-2.64 (1H, m), 2.30-2.20 (1H, m), 1.13 (3H, tr).

Example 46.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(piperidin-1-ylcarbonyl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-4'*(3'H)*-one

From Example 21 (50mg) and 1-piperidinecarbonyl chloride (0.02ml). The residue was purified by trituration with MeOH to yield the title compound as an off-white solid (2.8mg, 5%). TLC R_f 0.45 (10% MeOH/DCM). LCMS 426 $[M+H]^+$, RT 2.70 mins. ^1H NMR 300MHz (d_4-MeOH) 8.21 (1H, s), 8.20 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 4.01 (3H, s), 3.82-3.70 (2H, m), 3.64-3.50 (2H,

m), 3.37-3.20 (4H, m), 3.14 (3H, s), 2.69-2.57 (1H, m), 2.24-2.14 (1H, m), 1.69-1.52 (6H, m).

Example 46a.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-(piperidin-1-ylcarbonyl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one – Enatiomer 1

Example 21a (40mg), 1-piperidinecarbonyl chloride (0.013ml), DCM (20ml) and DIPEA (0.037ml) were combined under a nitrogen atmosphere and stirred at room temperature for 1.5 hours. The mixture was taken up in EtOAc (100ml) and washed with 1M HCl (30ml) and saturated aqueous Na_2CO_3 (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica eluting with 0-8% MeOH/DCM followed by preparative HPLC (Method A) to give the title compound as a solid (11mg, 25%).

Example 47 was prepared in a similar manner to the method of example 46a:-

Example 47.

1-(Isopropyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and isopropyl sulfonyl chloride (0.027ml). The residue was purified by column chromatography on silica eluting with EtOAc and then 5-10% MeOH/DCM followed by trituration with EtOAc:Heptane (1:5) to yield the title compound as a solid (4.1 mg, 3.8%). TLC R_f 0.56 (10% MeOH/DCM). LCMS 421 $[M+H]^+$, RT 2.60 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.19 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.78-3.54 (4H, m), 3.42-3.30 (1H, m), 3.19 (3H, s), 2.81-2.71 (1H, m), 2.34-2.22 (1H, m) 1.37 (3H, d), 1.34 (3H, d).

Example 48.

***iso*-Propyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

Intermediate 5 (100mg), dioxane (10ml), DMF (2ml), DIPEA (0.043ml) and isopropyl chloroformate (0.034ml) were combined and stirred at room temperature under a nitrogen atmosphere for 30 mins. The reaction mixture was diluted with EtOAc (100ml) and washed with aqueous Na_2CO_3 (30ml).

The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by trituration with EtOAc followed by column chromatography on silica eluting with EtOAc then 6-10% MeOH/DCM and trituration with EtOAc/heptane (1/8) twice to give the title compound (3mg, 3%). LCMS 401 $[M+H]^+$, RT 2.78 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.19 (1H, s), 7.4 (1H, s), 6.50 (1H, s), 4.95-4.8 (1H, m), 4.00 (3H, s), 3.75-3.55 (4H, m), 3.15 (3H, s), 2.75-2.55 (1H, m), 2.3-2.15 (1H, m) 1.35-1.20 (6H, m).

Example 49.

Ethyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

Intermediate 5 (100mg), ethyl chloroformate (0.028ml), DMF (10ml) and TEA (0.13ml) were combined and stirred at room temperature under a nitrogen atmosphere for 1 hour. The reaction mixture was concentrated *in vacuo* and the resulting residue purified by column chromatography on silica eluting with 0-10%MeOH/DCM. DMF had carried through this process and was removed by dissolving in DCM absorbing onto a solid phase cartridge, washing the DMF off with water followed by washing off the product with MeOH. The MeOH phase was concentrated *in vacuo* to afford the title compound as an off-white solid (8mg, 7%). TLC R_f 0.40 (10% MeOH/DCM). LCMS 387 $[M+H]^+$, RT 2.56 mins. ^1H NMR 400MHz (d_6-DMSO) 8.35 (1H, s), 8.00 (1H, s), 7.5 (1H, s, br), 7.3 (1H, s), 6.50 (1H, s), 4.15-4.0 (2H, m), 3.9 (3H, s), 3.6-3.4 (4H, m), 3.0 (3H, s), 2.1-2.0 (1H, m), 1.45-1.1 (4H, m).

Example 50.

Phenyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

Example 21 (50mg), phenyl chloroformate (0.018ml), DMF (10ml) and TEA (0.1ml) were combined and stirred at room temperature under a nitrogen atmosphere for 1 hour. The reaction mixture was concentrated *in vacuo* and the resulting residue purified by column chromatography on silica eluting with 0-10% MeOH/DCM. DMF had carried through this process and was removed by dissolving the residue in DCM, absorbing onto a solid phase cartridge, washing off the DMF with water followed by washing off the product with MeOH. The MeOH phase was evaporated *in vacuo* to afford the title

compound as a beige solid (6.5mg, 10%). LCMS 435 $[M+H]^+$, RT 3.03 mins. ^1H NMR 400MHz (d_6-DMSO) 8.35 (1H, s), 8.00 (1H, s), 7.65 (1H, d), 7.45-7.1 (5H, m), 6.55 (1H, d), 3.95 (3H, s), 3.9-3.5 (4H, m), 3.05 (3H, d), 2.7-2.5 (1H, m), 2.2-2.1 (1H, m).

Example 51.

Benzyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

Example 21 (50mg), benzyl chloroformate (0.02ml), DMF (5ml) and TEA (0.1ml) were combined and stirred at room temperature under a nitrogen atmosphere for 19 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue purified by column chromatography on silica eluting with 0-10%MeOH/DCM to afford the title compound as a beige solid (43mg, 67%). TLC R_f 0.275 (5% MeOH/DCM). LCMS 449 $[M+H]^+$, RT 3.14 mins. ^1H NMR 400MHz (d_6-DMSO) 8.35 (1H, s), 8.00 (1H, s), 7.55 (1H, d), 7.45-7.25 (6H, m), 6.5 (1H, s), 5.15-5.0 (2H, m), 3.9 (3H, s), 3.8-3.45 (4H, m), 3.0 (3H, s), 2.6-2.45 (1H, m), 2.15-2.0 (1H, m).

Example 52.

1-(3,3-Dimethyl-butyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

Acetic acid (22mg) was added to a stirred solution of Example 21 (60mg), sodium triacetoxyborohydride (400mg) and 3,3-dimethyl butyraldehyde (34mg) in MeOH (5ml) at 0°C under nitrogen. The mixture was allowed to warm to room temperature and was heated to 52°C for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was triturated with MeOH:Et_2O:Heptane. The filtrate was concentrated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as a solid (26mg, 42%). TLC R_f 0.63 (10% MeOH/DCM). LCMS 399 $[M+H]^+$, RT 1.78 mins. ^1H NMR 300MHz (d_4-MeOH) 8.22 (1H, s), 8.17 (1H, s), 7.36 (1H, s), 6.45 (1H, s), 4.01 (3H, s), 3.14 (1H, d), 3.16 (3H, s), 2.90-2.80 (2H, m), 2.79 (1H, d), 2.67-2.56 (2H, m), 2.55-2.50 (1H, m), 2.25-2.13 (1H, m), 1.53-1.46 (2H, m), 0.96 (9H, s).

Example 53.

1-(3,3-Dimethyl-2-oxobutyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

To a solution of Example 21 (75mg) and TEA (0.09ml) in THF (5ml) at 0°C, was added 1-bromopinacolone (0.04ml). The reaction mixture was stirred for 18 hours with slow warming to room temperature. The mixture was purified by column chromatography on silica eluting with 5%MeOH/DCM and the solid recovered was crystallised from MeOH/Et_2O to yield the title compound as a solid (4.6mg, 6%). HPLC RT 1.75 mins. LCMS 413 $[M+H]^+$, RT 1.76 mins. ^1H NMR 300MHz (d_4-MeOH) 8.22 (1H, s), 8.16 (1H, s), 7.45 (1H, s), 6.44 (1H, s), 6.74 (1H, s), 3.80-3.57 (2H, dd), 3.18 (3H, s), 3.16-3.10 (1H, d), 2.96-2.88 (1H, m), 2.82-2.76 (1H, d), 2.72-2.65 (1H, m), 2.52-2.42 (1H, m), 2.23-2.12 (1H, m), 1.18 (9H, s).

Example 54.

2-[7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]-*N,N*-dimethylacetamide

To a solution of Example 21 (50mg) and TEA (0.06ml) in THF (5ml) at 0°C, was added 2-chloro-*N,N*-dimethylacetamide (0.01ml). The reaction mixture was stirred for 18 hours with slow warming to room temperature. 2-chloro-*N,N*-dimethylacetamide (0.01ml) was added and the reaction mixture stirred at room temperature overnight. The mixture was concentrated *in vacuo* and purified by column chromatography on silica eluting with 5-10%MeOH/DCM to yield the title compound as a solid (20mg, 39%). TLC R_f 0.38 (10% MeOH/DCM). LCMS 400 $[M+H]^+$, RT 1.41 mins. ^1H NMR 300MHz (d_4-MeOH) 8.18 (1H, s), 8.17 (1H, s), 7.44 (1H, s), 6.44 (1H, s), 3.96 (3H, s), 3.55-3.35 (2H, dd), 3.28-3.20 (2H, m) 3.15 (3H, s), 3.10 (3H, s), 3.95 (3H, s), 2.90-2.70 (2H, m), 2.50-2.40 (1H, m), 2.23-2.12 (1H, m).

Example 55.

Cyclohexyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

To a solution of Example 21 (50mg) and TEA (0.1ml) in DCM (5ml) at room temperature, was added carbonic acid cyclohexylester 2,5-dioxo-pyrrolidin-1-yl ester (43mg) and the mixture stirred stirred for 18 hours at room temperature. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC (Method A) to yield the title compound as a solid (7.7mg, 12%). LCMS 441 $[M+H]^+$, RT 3.31 mins. ^1H NMR 400MHz (d_4-MeOH) 8.15

(2H, 2xs), 7.32 (1H, s), 6.44 (1H, s), 4.65-4.55 (1H, m), 3.90 (3H, s),3.68-3.56 (4H, m) 3.07 (3H, s), 2.60-2.54 (1H, m), 2.22-2.12 (1H, m), 1.90-1.15 (5H, m).

Examples 56-58 were prepared in a similar manner to the method of example 55:-

Example 56.

7'-Methoxy-3'-methyl-1-(morpholin-4-ylcarbonyl)-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 4-morpholine carbonyl chloride (0.02ml). The residue was purified by column chromatography on silica eluting with 3-5%MeOH/DCM to yield the title compound as a solid (20.6 mg, 37%). TLC R_f 0.44 (10% MeOH/DCM). LCMS 428 $[M+H]^+$, RT 2.22 mins. ^1H NMR 300MHz (d_4-MeOH) 8.18 (1H, s), 8.14 (1H, s), 7.32 (1H, s), 6.45 (1H, s), 3.96 (3H, s), 3.80-3.70 (2H, m), 3.68-3.60 (4H, m), 3.60-3.53 (2H, m), 3.35-3.20 (4H, m), 3.10 (3H, s) 2.65-2.55 (1H, m), 2.22-2.12 (1H, m).

Example 57.

***(3R)*-Tetrahydrofuran-3-yl (3-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}benzyl)carbamate**

From Example 43 (50mg) and carbonic acid 2,5-dioxo-pyrrolidin-1-yl ester tetrahydro-furan-3-*(S)*-yl ester (26mg). The residue was diluted with DCM (50ml), washed with 1M HCl (30ml) and washed with aqueous Na_2CO_3 solution (30ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (26mg, 41%). TLC R_f 0.53 (10% MeOH/DCM). LCMS 561 $[M+H]^+$, RT 2.42 mins. ^1H NMR 300MHz (d_6-DMSO) 8.30 (1H, d), 8.00 and 7.90 (1H, 2xs), 7.85 and 7.75 (1H, 2xm), 7.65 and 7.53 (1H, 2xs) 7.45-7.22 (5H, m), 6.46 (1H, s), 5.10-5.00 (1H, m) 4.22-4.15 (1H, m), 4.14-4.06 (1H, m), 3.90 (3H, m) 3.75-3.60 (8H, m), 3.00 (3H, m), 2.70-2.55 (1H, m), 2.18-2.00 (2H, m), 2.00-1.75 (1H, m).

Example 58.

1-(*tert*-Butoxycarbonyl)piperidin-4-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

From Example 21 (73mg) and 4-(2,5-dioxo-pyrrolidin-1-yloxycarbonyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester (71mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a solid (93 mg, 83%). TLC R_f 0.23 (5% MeOH/DCM). LCMS 542 $[M+H]^+$, RT 3.08 mins. ^1H NMR 400MHz (d_4-MeOH) 8.15 (2H, 2xs), 7.40 (1H, s), 6.45 (1H, s), 4.85-4.80 (1H, m), 3.95 (3H, s), 3.80-3.69 (6H, m), 3.11 (3H, s), 3.10-2.97 (2H, m) 2.70-2.60 (1H, m), 2.20-2.10 (1H, m), 1.90-1.80 (3H, m) 1.70-1.60 (1H, m), 1.40 (9H, s).

Example 59.

Piperidin-4-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

To a solution of Example 58 (73mg) in DCM (3ml) was added 1M HCl in Et_2O (3ml) and the mixture stirred at room temperature for 30mins. The precipitate formed was partitioned between 2M NaOH (20ml) and DCM (20ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a clear glass (35.5mg, 60%). LCMS 442 $[M+H]^+$, RT 1.55 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.15 (1H, s), 7.32 (1H, s), 6.45 (1H, s), 4.80-4.75 (1H, m), 3.95 (3H, s), 3.85-3.60 (4H, m), 3.10 (3H, s), 3.08-2.90 (2H, m) 2.75-2.55 (3H, m), 2.25-2.15 (1H, m), 2.00-1.75 (2H, m) 1.68-1.30 (2H, m).

Example 60.

1-Acetylpiperidin-4-yl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate

To a stirred solution of acetic acid (1 drop), HBTU (17mg) and TEA (2 drops) in DMF (2ml) was added after 5 mins Example 59 (19.5mg). The mixture was stirred for 3 hours then concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to yield the title compound as a solid (8.8mg, 41%). LCMS 484 $[M+H]^+$, RT 2.31 mins. ^1H NMR 400MHz (d_4-MeOH) 8.15 (1H, s), 8.12 (1H, s), 7.31 (1H, s), 6.45 (1H, s), 4.95-4.85 (1H, m), 3.97 (3H, s), 3.80-3.60 (6H, m), 3.50-3.32 (2H, m) 3.10 (3H, s), 2.70-2.60 (4H, m) 2.25-2.13 (1H, m), 2.10-2.00 (2H, m), 1.98-1.80 (2H, m).

Example 61.

(*3S*)-Tetrahydrofuran-3-yl (3-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}ethyl)carbamate

To a stirred solution of *N-tert*-butoxycarbonyl-beta-alanine (54mg) in DMF (5ml), at room temperature under nitrogen was added HBTU (108mg) and DIPEA (0.15ml). Example 21 (100mg), was added and the reaction stirred for 18 hours. The reaction mixture was concentrated *in vacuo*, dissolved in 1% MeOH/EtOAc (50ml) and washed with aqueous Na_2CO_3 solution (10ml) and 1M HCl solution (10ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica eluting with 3% MeOH/DCM afforded a brown solid. This was dissolved in a solution of 1M HCl in Et_2O (5ml) and the mixture stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* to yield a brown oil which was dissolved in THF/H_2O (2.5ml/2.5ml). To this was added $NaHCO_3$ (35mg) and carbonic acid 2,5-dioxo-pyrrolidin-1-yl ester tetrahydro-furan-3(*S*)-yl ester (40mg). After stirring for 16 hours at room temperature, the THF was removed *in vacuo* and the aqueous residue partitioned between water (10ml) and 10%MeOH/DCM (10ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica eluting with 5-10%MeOH/DCM afforded the title compound as a brown solid 65mg (48%). TLC R_f 0.12 (5% MeOH/DCM). LCMS 500 $[M+H]^+$, RT 2.16 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.34 (1H, s), 6.45 (1H, d), 5.22-5.10 (1H, m), 3.95 (3H, s), 3.90-3.60 (8H, m), 3.45-3.35 (2H, m) 3.13 (3H, d), 2.75-2.52 (2H, m) 2.50-2.42 (1H, m), 2.32-1.90 (3H, m).

Example 62.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-phenyl-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

To a solution of aniline (0.02ml) in dry DCM (15ml) under nitrogen cooled to –78°C was added triphosgene (19mg) followed by TEA (0.05ml). The mixture was allowed to warm to 0°C and stirred for 30mins. Addition of Example 21 (70mg) then took place along with more TEA (0.05ml). The reaction mixture

was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with DCM (15ml) and successively washed with 1M aqueous HCl (2x15ml), H_2O (15ml), $NaHCO_3$ solution (2x15ml) and brine (15ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with EtOAc then 10% MeOH/DCM followed by trituration in MeOH/pentane to afford the title compound as a white solid (7.4mg, 9%). TLC R_f 0.44 (10% MeOH/DCM). LCMS 434 $[M+H]^+$, RT 2.74 mins. ^1H NMR 300MHz (d_4-MeOH) 8.23 (1H, s), 8.14 (1H, s), 7.31-7.25 (2H, tr), 7.28-7.23 (2H, tr), 7.04-6.99 (1H, tr), 6.50 (1H, s), 3.97 (3H, s), 3.83-3.70 (4H, m), 3.16 (3H, s), 2.77-2.63 (1H, m), 2.34-2.24 (1H, m).

Examples 63-83 were prepared in a similar manner to the method of example 62:-

Example 63.

7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-phenyl-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (70mg) and *N*-methylaniline (0.02ml). Purification by trituration in EtOAc/pentane afforded the title compound as a green solid (26mg, 32%). TLC R_f 0.15 (EtOAc). LCMS 448 $[M+H]^+$, RT 2.87 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.11 (1H, s), 7.40-7.33 (3H, m), 7.20-7.15 (3H, m), 6.43 (1H, s), 3.98 (3H, s), 3.52-3.23 (4H, m), 3.19 (3H, s), 2.94 (3H, s), 2.53-2.41 (1H, m), 2.09-1.98 (1H, m).

Example 64.

1-{[4-(4-Chlorophenoxy)piperidin-1-yl]carbonyl}-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 4-(4-chlorophenoxy)-piperidine (32mg). Purification by column chromatography on silica eluting with 5-10% MeOH/DCM followed by trituration in DCM/pentane afforded the title compound as a yellow solid (15mg, 21%). TLC R_f 0.47 (10%MeOH/DCM). LCMS 554 $[M+H]^+$, RT 3.54 mins. ^1H NMR 300MHz (d_4-MeOH) 8.23 (1H, s), 7.40 (1H, s), 7.30-7.26 (2H, d), 7.07-6.94 (2H, d), 6.52 (1H, s), 4.60-4.50 (1H, m), 4.02 (3H, s), 3.84-3.77 (2H, m), 3.67-3.53 (4H, m), 3.17 (3H, s), 2.73-2.59 (1H, m), 2.26-2.1 6 (1H, m), 2.17-1.83 (1H, m), 1.82-1.64 (1H, m).

Example 65.

***N*-Benzyl-7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and *N*-benzylmethylamine (0.017ml). Purification by column chromatography on silica eluting with 5% MeOH/DCM followed by trituration in DCM/pentane afforded the title compound as an off-white solid (31mg, 52%). TLC R_f 0.52 (10%MeOH/DCM). LCMS 462 $[M+H]^+$, RT 2.94 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.18 (1H, s), 8.14 (1H, s), 7.36 (1H, s), 7.25-7.21 (2H, d), 6.47 (1H, s), 4.52-4.47 (1H, d), 4.35-4.30 (1H, d), 3.95 (3H, s), 3.97-3.77 (1H, m), 3.68-3.52 (4H, m), 3.10 (3H, s), 2.77 (3H, s), 2.67-2.56 (1H, m), 2.20-2.10 (1H, m).

Example 66.

***N,N*-Diethyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (100mg) 4-piperidone monohydrate hrdyochloride (40mg) and TEA (0.17ml). Purification by column chromatography on silica eluting with 5% MeOH/DCM followed by trituration in DCM/pentane afforded the title compound as a magnolia solid (58mg, 54%). TLC R_f 0.47 (10%MeOH/DCM). LCMS 414 $[M+H]^+$, RT 2.67 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.17 (2H, 2xs), 7.35 (1H, s), 6.47 (1H, s), 3.98 (3H, s), 3.79-3.71 (2H, m), 3.60-3.50 (2H, m), 3.30-3.21 (4H, m), 3.13 (3H, s), 2.69-2.56 (1H, m), 2.21-2.11 (1H, m), 1.15-1.10 (1H, tr).

Example 67.

7'-Methoxy-3'-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (100mg) and methylpiperazine (0.01ml). The product in DCM (15ml) was extracted with 1M HCL (2x15ml), the aqueous layers were combined, basified with solid NaOH and extracted with DCM (3x20ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated in DCM/pentane and further purified by preparative HPLC (Method A) to afford the title compound as a yellow solid (5.6mg, 10%). TLC R_f 0.08 (10%MeOH/DCM). LCMS 441 $[M+H]^+$, RT 1.48 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.19 (2H, 2xs), 7.36 (1H, s), 6.48 (1H, s),

3.97 (3H, s), 3.79-3.74 (2H, m), 3.63-3.52 (2H, m), 3.40-3.28 (4H, m), 3.13 (3H, s), 2.66-2.58 (1H, m), 2.46-2.40 (4H, m), 2.29 (3H, s), 2.22-2.13 (1H, m).

Example 68.

***N*-(2,4-Difluorophenyl)-7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (100mg) and 2,4-difluoro-*N*-methylaniline (18.6mg). Purification by trituration in DCM/pentane afforded the title compound as a white solid (26mg, 41%). TLC R_f 0.47 (10%MeOH/DCM). LCMS 484 $[M+H]^+$, RT 2.93 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.17 (1H, s), 8.11 (1H, s), 7.36-7.27 (1H, m), 7.34 (1H, s), 7.10-6.93 (2H, m), 6.40 (1H, s), 3.96 (3H, s), 3.50-3.40 (1H, m), 3.36-3.24 (3H, m), 3.10 (3H, s), 2.96 (3H, s), 2.56-2.45 (1H, m), 2.09-2.00 (1H, m).

Example 69.

***tert*-Butyl 4-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}piperazine-1-carboxylate**

From Example 21 (100mg) and *t*-butyl-1-piperazine (48.4mg). Purification by column chromatography on silica eluting with 5% MeOH/DCM and trituration with DCM/pentane yielded the title compound as a yellow solid (34.5mg, 25%). TLC R_f 0.59 (10% MeOH/DCM). LCMS 527 $[M+H]^+$, RT 3.01 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.3 (2H, 2xs), 7.40 (1H, s), 6.50 (1H, s), 4.05 (3H, s), 3.85-3.75 (2H, m), 3.80-3.65 (2H, m), 3.50-3.40 (4H, m), 3.40-3.25 (4H, m), 3.15 (3H, s), 2.70-2.60 (1H, m), 2.25-2.15 (1H, m), 1.45 (9H, s).

Example 70.

***N*-(2-Chlorophenyl)-7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and 2-chloro-*N*-methylaniline (18.2mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a solid (11mg, 18%). TLC R_f 0.23 (5% MeOH/DCM). LCMS 482 $[M+H]^+$, RT 2.95 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.50-7.20 (5H, m), 6.45 (1H, s), 4.00 (3H, s), 3.50-3.40 (1H, m), 3.35-3.10 (3H, m), 3.10 (3H, s), 2.95 (3H, s), 2.55-2.40 (1H, m), 2.10-2.00 (1H, m).

Example 71.

7'-Ethoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-[2-(trifluoromethoxy)phenyl]-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2-trifluoromethoxy-*N*-methylaniline (24.9mg). The precipitate was collected and dried to yield the title compound as a light brown solid (32.3mg, 47%). TLC R_f 0.31 (10% MeOH/DCM). LCMS 532 $[M+H]^+$, RT 3.16 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.45-7.30 (5H, m), 6.40 (1H, s), 3.95 (3H, s), 3.55-3.45 (1H, m), 3.40-3.25 (2H, m), 3.20-3.10 (4H, m), 2.95 (3H, s), 2.55-2.45 (1H, m), 2.10-2.00 (1H, m).

Example 72.

1-{[4-(2-Fluorophenyl)piperidin-1-yl]carbonyl}-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 4-(2-fluorophenyl)piperidine (23mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a white solid (29mg, 43%). LCMS 520 $[M+H]^+$, RT 3.31 mins. ^1H NMR 300MHz (d_4-MeOH) 8.25 (2H, s), 7.40 (1H, s), 7.25-7.15 (2H, m), 7.10-7.00 (2H, m), 6.55 (1H, s), 4.00 (3H, s), 4.00-3.75 (4H, m), 3.65-3.55 (2H, m), 3.15 (3H, s), 3.15-2.85 (3H, m), 2.70-2.60 (1H, m), 2.25-2.15 (1H, m), 1.85-1.60 (4H, m).

Example 73.

7'-Methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-[2-(trifluoromethyl)phenyl]-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2-(methylamino) benzotrifluoride (23mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a solid (8.5mg, 13%). TLC R_f 0.18 (5% MeOH/DCM). LCMS 516 $[M+H]^+$, RT 3.01 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.75-7.60 (2H, m), 7.35-7.50 (3H, m), 6.40 (1H, s), 3.95 (3H, s), 3.80-3.35 (2H, m), 3.25-3.10 (5H, m), 2.95 (3H, s), 2.55-2.35 (1H, m), 2.10-2.00 (1H, m).

Example 74.

Methyl 4-[{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}(methyl)amino]benzoate

From Example 21 (500mg) and methyl-4-(methylamino)benzoate (215mg). Trituration with DCM/pentane afforded the title compound as a yellow solid (484mg, 74%). TLC R_f 0.53 (10% MeOH/DCM). LCMS 506 $[M+H]^+$, RT 2.78 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.95 (2H, d), 7.45 (1H, s), 7.35 (2H, d), 6.45 (1H, s), 4.05 (3H, s), 3.85 (3H, s), 3.60-3.50 (2H, m), 3.25 (3H, s), 3.00 (3H, s), 2.65-2.55 (1H, m), 2.15-2.05 (1H, m).

Example 75.

7'-Methoxy-*N*-(4-methoxyphenyl)-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and *N*-methyl-*p*-anisidine (18mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a pale green solid (15mg, 24%). TLC R_f 0.44 (10% MeOH/DCM). LCMS 478 $[M+H]^+$, RT 2.79 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.10 (1H, s), 7.35 (1H, s), 7.10 (2H, d), 6.85 (2H, d), 6.40 (1H, s), 4.00 (3H, s), 3.70 (3H, s), 3.55-3.35 (2H, m), 3.20 (2H, m), 3.1 0 (3H, s), 2.95 (3H, s), 2.50-2.40 (1H, m), 2.05-1.95 (1H, m).

Example 76.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-{[4-(pyridin-4-yloxy)piperidin-1-yl]carbonyl}-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 4-(piperidin-4-yloxy)-pyridine (CAS 224178-65-8) (46mg). The residue was purified by column chromatography on silica eluting with 7% MeOH/DCM, followed by preparative HPLC (Method B) to yield the title compound as a solid (10mg, 15%). LCMS 519 $[M+H]^+$, RT 1.64 mins. ^{1}H NMR 400MHz (d_4-MeOH) 8.35 (2H, 2xs), 8.20 (1H, s), 8.18 (1H, s), 7.35 (1H, s), 7.1 0 (1H, s), 7.05 (1H, s), 6.50 (1H, s), 4.75 (1H, m), 3.95 (3H, s), 3.80-3.75 (2H, m), 3.60-3.50 (4H, m), 3.30-3.20 (2H, m), 3.15 (3H, s), 2.65-2.55 (1H, m), 2.20-2.10 (1H, m), 2.05-1.95 (2H, m), 1.80-1.65 (2H, m).

Example 77.

1-{[4-(1-Benzofuran-2-yl)piperidin-1-yl]carbonyl}-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 4-(2-benzofuranyl)-piperidine (CAS 54477-05-3) (26mg). The residue was purified by column chromatography on silica eluting with 30-100% EtOAc/heptane followed by 5% MeOH/DCM. Trituration in DCM/pentane afforded the title compound as a yellow solid (4mg, 6%). TLC R_f 0.44 (EtOAc). LCMS 5427 $[M+H]^+$, RT 3.53 mins. ^1H NMR 400MHz (d_4-MeOH) 8.15 (1H, s), 7.45 (1H, d), 7.35 (2H, m), 7.20-7.10 (2H, m), 6.50 (1H, s), 6.45 (1H, s), 3.95 (3H, s), 3.90-3.55 (4H, m), 3.65-3.55 (2H, m), 3.15 (3H, s), 3.05-2.95 (3H, m), 2.65-2.55 (1H, m), 2.25-2.15 (1H, m), 2.15-2.05 (2H, m), 1.75-1.60 (2H, m).

Example 78.

7'-Methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-pyridin-2-yl-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2-(methylamino)pyridine (0.013ml). The residue was purified by column chromatography on silica eluting with 4% MeOH/DCM to yield the title compound as a solid (9.2mg, 16%). LCMS 449 $[M+H]^+$, RT 2.33 mins. ^1H NMR 400MHz (d_4-MeOH) 8.30 (1H, d), 8.15 (1H, s), 8.10 (1H, s), 7.75 (1H, t), 7.30 (1H, s), 7.15 (1H, d), 7.05 (1H, t), 6.45 (1H, s), 3.95 (3H, s), 3.65-3.35 (4H, m), 3.25 (3H, s), 3.05 (3H, s), 2.60-2.50 (1H, m), 2.15-2.05 (1H, m).

Example 79.

***N*-(2-Cyanoethyl)-7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and *N*-methyl-β-alanine nitrile (0.01ml). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a yellow solid (30mg, 50%). TLC R_f 0.46 (10% MeOH/DCM). LCMS 425 $[M+H]^+$, RT 2.28 mins. ^1H NMR 400MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.80-3.70 (2H, m), 3.60-3.50 (3H, m), 3.45-3.35 (1H, m), 3.10 (3H, s), 3.00 (3H, s), 2.75-2.70 (2H, t), 2.65-2.60 (1H, m), 2.20-2.10 (1H, m).

Example 80.

***N*-Ethyl-*N*-isopropyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg) and *N*-ethylisopropylamine (34mg). The residue was purified by column chromatography on silica eluting with 3% MeOH/DCM followed by dissolving in DCM (50ml) and washing with aqueous 10% Na_2CO_3 (20ml), 1M HCl (aq) (20ml) and water (20ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a solid (8.5mg, 11%). LCMS 428 $[M+H]^+$, RT 2.81 mins. ^1H NMR 400MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.45 (1H, s), 4.00 (3H, s), 3.95-3.85 (1H, m), 3.80-3.70 (2H, m), 3.60-3.50 (2H, m), 3.25-3.15 (1H, m), 3.10 (3H, s), 3.10-3.00 (1H, m), 2.65-2.55 (1H, m), 2.20-2.10 (1H, m), 1.20-1.10 (6H, m), 1.05-1.00 (3H, t).

Example 80a.

***N*-Ethyl-*N*-isopropyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (70mg) and *N*-ethylisopropylamine (34mg). The residue was purified by preparative HPLC (method A) to yield the title compound as a solid (2.5mg, 3.3%). LCMS 428 $[M+H]^+$, RT 2.79 mins. ^1H NMR 400MHz (d_4-MeOD) 8.20 (1H, s), 8.15 (1H, s), 7.35 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.85-3.95 (1H, m), 3.65-3.75 (2H, m), 3.45-3.55 (2H, m), 3.25-3.15 (1H, m), 3.15-3.00 (1H, m), 3.10 (3H, s), 2.65-2.55 (1H, m), 2.20-2.10 (1H, m), 1.15-1.10 (6H, m), 1.05 (3H, t).

Example 81.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-(2,2,2-trifluoroethyl)-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2,2,2-trifluoroethylamine (19mg). The residue was purified by column chromatography on silica eluting with 5-10% MeOH/DCM to yield the title compound as an off-white solid (7.5mg, 13%). TLC R_f 0.21 (10% MeOH/DCM). LCMS 440 $[M+H]^+$, RT 2.46 mins. ^1H NMR 400MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.85 (2H, q), 3.65 (4H, m), 3.10 (3H, s), 2.75-2.65 (1H, m), 2.25-2.15 (1H, s).

Example 82.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-pyrimidin-2-yl-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and 2-aminopyrimidine (13mg). The residue was purified by column chromatography on silica eluting with 7% MeOH/DCM

followed by preparative HPLC (Method B) to yield the title compound as a solid (1.5mg, 2.7%). TLC R_f 0.05 (5% MeOH/DCM). LCMS 436 $[M+H]^+$, RT 1.96 mins. ^1H NMR 400MHz (d_4-MeOH) 8.50 (2H, 2xs), 8.20 (2H, 2xs), 7.35 (1H, s), 7.05 (1H, t), 6.50 (1H, s), 4.00 (3H, s), 3.85-3.75 (4H, m), 3.20 (3H, s), 2.80-2.70 (1H, m), 2.30-2.25 (1H, m).

Example 83.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-{[4-(trifluoromethyl)piperidin-1-yl]carbonyl}-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

From Example 21 (50mg) and 4-(trifluoromethyl)piperidine (20mg). The residue was purified by column chromatography on silica eluting with 3-5% MeOH/DCM to yield the title compound as a yellow solid (27mg, 41%). TLC R_f 0.67 (10% MeOH/DCM). LCMS 494 $[M+H]^+$, RT 3.00 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.85-3.70 (4H, m), 3.65-3.50 (2H, m), 3.15 (3H, s), 3.00-2.75 (2H, m), 2.70-2.55 (1H, m), 2.50-2.30 (1H, m), 2.25-2.15 (1H, m), 1.90-1.80 (2H, m), 1.60-1.40 (2H, m).

Example 84.

4-[{[7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}(methyl)amino]benzoic acid

Example 74 (484mg), $LiOH.H_2O$ (161mg), THF (18ml), MeOH (9ml) and water (9ml) were combined and stirred at room temperature for 18 hours. The solvents were removed *in vacuo* and the residue triturated with 2N HCl to afford the title compound as a yellow solid (420mg). TLC R_f 0.17 (EtOAc). LCMS 492 $[M+H]^+$, RT 2.39 mins. ^1H NMR 300MHz (d_4-MeOH) 8.15 (1H, s), 8.1 (1H, s), 7.95 (2H, d), 7.3 (1H, s), 7.2 (2H, d), 6.4 (1H, s), 3.95 (3H, s), 3.5-3.25 (4H, m), 3.2 (3H, s), 3.0 (3H, s), 2.6-2.45 (1H, m), 2.1-2.0 (1H, m).

Example 85.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-1-pyridin-2-yl-*1'H*-spiro[pyrrolidine-3,2'-quinazolin]-4'*(3'H)*-one

Example 21 (35mg), 2-chloropyridine, DBN (0.045ml) and DMF (3ml) were combined and heated to 120°C for 1.5 hours in a microwave reactor. The solvents were then removed *in vacuo* and the residue purified by preparative HPLC (Method A) to give the title compound as a glass (3mg). LCMS 392

$[M+H]^+$, RT 1.57 mins. ^1H NMR 300MHz (d_4-MeOH) 8.45 (1H, s), 8.17 (1H, s), 8.15 (1H, s), 8.02 (1H, d), 7.55 (1H, m), 7.3 (1H, s), 6.65 (1H, m), 6.55 (1H, d), 6.45 (1H, s), 3.95 (3H, s), 3.85-3.65 (4H, m), 2.85-2.75 (1H, m), 2.35-2.3 (1H, m).

Example 86.

***N*-Allyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

To a solution of Example 21 (70mg) in DCM (5ml) was added allyl isocyante (0.017) and DIPEA (0.07ml). The reaction was stirred overnight and concentrated *in vacuo.* The residue was dissolved in DCM (100ml) and washed with 1N aqueous HCl (25ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The resulting residue was triturated with Et_2O to yield the title compound as a solid (49mg, 65%). TLC R_f 0.12 (5% MeOH/DCM). LCMS 398 $[M+H]^+$, RT 2.26 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 5.91-5.79 (1H, m), 5.17-5.11 (1H, m), 5.06-5.03 (1H, m), 4.0 (3H, s), 3.79-3.74 (2H, m), 3.66-3.60 (4H, m), 3.12 (3H, s), 2.75-2.62 (1H, m), 2.27-2.16 (1H, m).

Examples 87 – 90 were prepared in a similar manner to the method of example 86:-

Example 87.

***N*-Cyclopentyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg), DCM (5ml), cyclopentyl isocyanate (0.021ml) and DIPEA (0.07ml) to yield the title compound as a solid (60mg, 75%). TLC R_f 0.15 (5% MeOH/DCM). LCMS 426 $[M+H]^+$, RT 2.60 mins. ^1H NMR 300MHz (d_4-MeOH) 8.13 (1H, s), 8.13 (1H, s), 7.30 (1H, s), 6.46, (1H, s), 4.05-3.95 (1H, m), 3.92 (3H, s), 3.65-3.55 (4H, m), 3.10 (3H, s), 2.74-2.54 (1H, m), 2.25-2.12 (1H, m), 1.95-1.87 (2H, m), 1.74-1.30 (6H, m).

Example 88.

Ethyl *N*-{[7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazolin]-1-yl]carbonyl}glycinate

From Example 21 (70mg), DCM (5ml), ethyl isocyanatoacetate (0.021ml) and DIPEA (0.07ml) to yield the title compound as a solid (49mg, 58%). TLC R_f

0.12 (5% MeOH/DCM). LCMS 444 $[M+H]^+$, RT 2.26 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (1H, s), 8.20 (1H, s), 7.38 (1H, s), 6.50 (1H, s), 4.25-4.15 (2H, q), 4.0 (3H, s), 3.88 (2H, s), 3.70-3.65 (4H, m), 3.17 (3H, s), 2.78-2.62 (1H, m), 2.30-2.20 (1H, m), 1.29-1.22 (3H, t).

Example 89.

***N*-Benzoyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg), DCM (5ml), benzoyl isocyanate (0.024ml) and DIPEA (0.07ml) to yield the title compound as a solid (57mg, 65%). TLC R_f 0.13 (5% MeOH/DCM). LCMS 462 $[M+H]^+$, RT 2.50 mins. ^1H NMR 300MHz (d_6-DMSO) 8.31 (1H, s), 7.99 (1H, s), 7.90-7.70 (2H, m), 7.65-7.55 (2H,m), 7.50-7.40 (2H, m), 7.32 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.95-3.55 (4H, m), 3.00 (3H, s), 2.65-2.55 (1H, m), 2.18-2.05 (1H, m).

Example 90.

***N*-(3,5-Dimethylisoxazol-4-yl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (70mg), DCM (5ml), 3,5-dimethyl isoxazol-4-yl isocyanate (26mg) and DIPEA (0.07ml) to yield the title compound as a solid (19mg, 22%). TLC R_f 0.09 (5% MeOH/DCM). LCMS 453 $[M+H]^+$, RT 2.22 mins. ^1H NMR 300MHz (d_4-MeOH) 8.21 (1H, s), 8.21 (1H, s), 7.35 (1H, s), 6.52 (1H, s), 4.00 (3H, s), 3.75 (4H, m), 3.18 (3H, s), 2.85-2.65 (1H, m), 2.32-2.26 (1H, m), 2.28 (3H, s), 2.15(3H, s).

Examples 91-99 were prepared in a similar manner to the method of example 62:-

Example 91.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-3-thienyl-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (25mg) and 3-aminothiophene (12mg). The resulting solid was obtained by filtration to yield the title compound as a white solid (10.1mg, 33%). LCMS 440 $[M+H]^+$, RT 2.64 mins. ^1H NMR 300MHz (d_6-DMSO) 8.65 (1H, s), 8.40 (1H, s), 8.05 (1H, s), 7.60 (1H, s), 7.40 (2H, m), 7.30 (1H, d),

7.15 (1H, d), 6.60 (1H, s), 3.95 (3H, s), 3.70-3.60 (4H, m), 3.10 (3H, s), 2.75-2.60 (1H, m), 2.20-2.10 (1H, m).

Example 92.

***N*-(Cyclopropylmethyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21 (50mg) and aminomethylcyclopropane (11□l). The residue was purified by preparative HPLC (Method B) to yield the title compound as a white solid (20mg, 37%). TLC R_f 0.11 (5% MeOH/DCM). LCMS 412 $[M+H]^+$, RT 2.39 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20(2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.60-3.70 (2H, m), 3.15 (3H, s), 3.05 (2H, d), 2.60- 2.80 (1H, m), 0.90-1.10 (1H, m), 0.40-0.50 (2H, m), 0.10-0.20 (2H, m).

Example 93.

7'-Methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-*N*-(2-phenylethyl)-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (50mg) and *N*-methylphenethylamine (18mg) using pyridine (33mg). The residue was purified by column chromatography on silica eluting with 2-4% MeOH/DCM followed by preparative HPLC (Method B) to yield the title compound as a white solid (2.3mg, 15%). TLC R_f 0.43 (5% MeOH/DCM). LCMS 476 $[M+H]^+$, RT 2.98 mins. ^1H NMR 300MHz (d_4-MeOH) 8.15(2H, 2xs), 7.35 (1H, s), 7.05-7.20 (5H, m), 6.55 (1H, s), 3.95 (3H, s), 3.50-3.70 (3H, m), 3.25-3.45 (3H, m), 3.10 (3H, s), 2.75—2.85 (4H, m), 2.45-2.60 (1H, m), 2.05-2.15 (2H, m).

Example 94.

7'-Methoxy-*N*,3'-dimethyl-*N*-[2-(methylsulfonyl)ethyl]-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide

From Example 21 (80mg) and (2-methanesulfonyl-ethyl)methylamine (CAS 202198-18-3) (28mg) using pyridine (33mg). The residue was purified by preparative HPLC (Method B) to yield the title compound as a white solid (9mg, 9%). LCMS 478 $[M+H]^+$, RT 2.12 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.35 (1H, s), 6.50 (1H, s), 3.95 (3H, s), 3.55-3.85 (4H, m), 3.35-3.45 (4H, m), 3.15 (3H, s), 2.95 (6H, 2xs), 2.55-2.70 (1H, m), 2.10-2.25 (2H, m).

Example 95.

***N*,7'-Dimethoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (80mg) and *N,O*-dimethylhydroxylamine hydrochloride (22mg) using diisopropylethylamine (141mg). The residue was by preparative HPLC (Method A) to yield the title compound as a white solid (27.7mg, 32%). TLC R_f 0.37 (5% MeOH/DCM). LCMS 402 $[M+H]^+$, RT 2.37 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (2H, s), 7.40 (1H, s), 6.50 (1H, s), 4.00 (3H, s), 3.70-3.90 (4H, m), 3.65 (3H, s), 3.20 (3H, s), 3.00 (3H, s), 2.60-2.75 (1H, m), 2.15-2.35 (2H, m).

Example 96.

***N*-[2-(Dimethylamino)ethyl]-7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (50mg) and *N,N,N'*-trimethylethylenediamine (13mg). The residue was purified by column chromatography on silica eluting with DCM/MeOH/c.NH_4OH (90:9:1) to give the title compound as a pale green glass (3.2mg, 6%). TLC R_f 0.32 (9% MeOH/DCM + trace c.NH_4OH). LCMS 443 $[M+H]^+$, RT 1.50 mins. ^1H NMR 300MHz (d_4-MeOH) 8.17-8.18 (2H, 2 x s), 7.32 (1H, s), 6.47 (1H, s), 3.97 (3H, s), 3.33-3.82 (6H, m), 3.12 (3H, s), 2.90 (3H, s), 2.56-2.67 (1H, m), 2.51 (2H, t), 2.26 (3H, s), 2.10-2.20 (1H, m).

Example 97.

***N*-Cyclopropyl-*N*-ethyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (50mg) and the hydrochloride salt of *N*-cyclopropyl-*N*-ethylamine (CAS 26389-72-0) (16mg). The residue was purified by preparative HPLC (Method B) to give the title compound (11mg, 20%). TLC R_f 0.35 (10% MeOH/DCM). LCMS 426 $[M+H]^+$, RT 2.60 mins. ^1H NMR 300MHz ($CDCl_3$) 8.32 (1H, s), 7.88 (1H, s), 7.48 (1H, s), 6.24 (1H, s), 5.00 (1H, brs), 3.75-3.92 (4H, m), 3.40-3.65 (4H, m), 3.06-3.18 (4H, m), 2.45-2.58 (2H, m), 2.14-2.23 (1H, m), 1.11 (3H, t), 0.60-0.88 (4H, m).

Example 98.

***N*-(2-Cyanoethyl)-*N*-isopropyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (53mg) and 3-(isopropylamino)propionitrile (CAS 692-98-8) (16mg). The residue was purified by preparative HPLC (Method B) to give the title compound (43mg, 68%). LCMS 453 $[M+H]^+$, RT 2.53 mins. ^1H NMR 300MHz ($CDCl_3$) 8.32 (1H, s), 7.87 (1H, s), 7.38 (1H, s), 6.27 (1H, s), 4.92 (1H, s), 3.93 (3H, s), 3.75-3.86 (4H, m), 3.42-3.59 (2H, m), 3.20-3.30 (1H, m), 3.16 (3H, s), 2.60-2.65 (2H, m), 2.41-2.52 (1H, m), 2.20-2.29 (1H, m), 1.20 (3H, d), 1.17 (3H, d).

Example 99.

***N*-[2-(Acetylamino)ethyl]-7'-methoxy-*N*,3'-dimethyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxamide**

From Example 21a (50mg) and *N*-[2-(methylamino)ethyl]acetamide (CAS 4814-81-7) (15mg). The residue was purified by preparative HPLC (Method B) to give the title compound (19mg, 32%). TLC R_f 0.45 (10% MeOH/DCM). LCMS 457 $[M+H]^+$, RT 2.01 mins. ^1H NMR 300MHz (d_4-MeOH) 8.2 (2H, 2 x s), 7.36 (1H, s), 6.52 (1H, s), 3.99 (3H, s), 3.70-3.80 (2H, m), 3.53-3.62 (2H, m), 3.24-3.46 (4H, m), 3.15 (3H, s), 2.91 (3H, s), 2.57-2.68 (1H, m), 2.15-2.23 (1H, m), 1.89 (3H, s).

Example 100.

7'-Methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H,2H*-spiro[pyrrolidine-3,2'-quinazoline]-2,4'(*3'H*)-dione

To a solution of Intermediate 6 (25mg) in MeOH (10ml) was added a catalytic amount of 10% Pd/C. The solution was stirred at room temperature under hydrogen for 3.5 hours. The reaction mixture was filtered to remove catalyst and solvents removed under reduced pressure to give the title compound (18mg, 100%). LCMS 329 $[M+H]^+$, RT 1.93 mins.

Example 101.

1-Benzyl-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-*1'H,2H*-spiro[pyrrolidine-3,2'-quinazoline]-2,4'(*3'H*)-dione

To a solution of Example 100 (90mg) in DMF (10ml) was added sodium hydride (11mg). The solution was stirred under nitrogen for 90 mins at which point benzylbromide (0.03ml) was added. The solution was stirred for 18 hours. The solvents were removed *in vacuo* and the product purified by preparative HPLC (Method A) to give the title compound as a beige solid (11mg, 10%). LCMS

419 $[M+H]^+$, RT 2.81 mins. ^1H NMR 400MHz (d_4-MeOD) 8.15 (1H, s), 8.10 (1H, s), 7.40-7.30 (6H, m), 6.35 (1H, s), 4.60 (1H, d), 4.40 (1H, d), 3.95 (3H, s), 3.50-3.30 (2H, m), 2.90 (3H, s), 2.75-2.65 (1H, m), 2.35-2.25 (1H, m).

Examples 102, 103 and 104 describe the preparation of three out of the four diastereomers of 1-*tert*-butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate.

Example 102.

1-*tert*-Butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate (Diastereomer 1)

To a solution of Intermediate 1 (300mg) in dry DCE (30ml) under nitrogen was added 1-*tert*-butyl 2-methyl (*2S*)-4-oxopyrrolidine-1,2-dicarboxylate (300mg) and PTSA (5mg). The mixture was heated at reflux for 5 hours. The reaction mixture was diluted with DCM (100ml) and washed with H_2O (50ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with EtOAc to afford the title compound along with Example 103 as a pale yellow solid (420mg, 73%). A portion of this mixture was separated into its component diastereomers by preparative HPLC (Method A) to afford Diastereomer 1 as a cream solid (197mg). TLC R_f 0.29 (EtOAc). LCMS 473 $[M+H]^+$, RT 3.25 mins. ^1H NMR 300MHz (d_4-MeOH) 8.21 (1H, s), 8.18 (1H, s), 7.38 (1H, s), 6.41 (1H, s), 4.54-4.48 (1H, dd), 4.05-4.02 (1H, d), 4.02 (3H, s), 3.80 (3H, s), 3.72-3.68 (1H, d), 3.12 (3H, s), 3.04-2.88 (1H, m), 2.35-2.25 (1H, m), 1.49 and 1.45 (9H, 2xs).

Example 103.

1-*tert*-Butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate (Diastereomer 2)

Following the procedure described for Example 102; Diastereomer 2 was also isolated as an off-white solid (41mg). TLC R_f 0.29 (EtOAc). LCMS 473 $[M+H]^+$, RT 3.15 mins. ^1H NMR 300MHz (d_4-MeOH) 8.21 (1H, s), 8.19 (1H,

s), 7.38 (1H, s), 6.51 (1H, s), 4.57-4.50 (1H, m), 4.00 (3H, s), 3.83 (3H, s), 3.83-3.72 (2H, m), 3.15 (3H, s), 2.67-2.50 (2H, m), 1.45 (9H, s).

Example 104.

1-*tert*-Butyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate (Diastereomer 3)

A solution of Intermediate 1 (700mg), 1-*tert*-butyl 2-methyl-(*2R*)-4-oxopyrrolidine-1,2-dicarboxylate (CAS 256487-77-1) (720mg) and PTSA (5mg) in dry DCE (40ml) was heated at reflux for 18 hours. The reaction mixture was diluted with DCM (100ml) and washed with aqueous 2M HCl (40ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method A) to afford Diastereomer 3 as a single diastereomer as an off-white solid (635mg, 47%). TLC R_f 0.35 (EtOAc). LCMS 473 $[M+H]^+$, RT 3.26 mins. ^1H NMR 300MHz (d_4-MeOH) 8.21 (1H, s), 8.18 (1H, s), 7.38 (1H, s), 6.41 (1H, s), 4.54-4.48 (1H, dd), 4.05-4.02 (1H, d), 4.02 (3H, s), 3.80 (3H, s), 3.72-3.68 (1H, d), 3.12 (3H, s), 3.04-2.88 (1H, m), 2.35-2.25 (1H, m), 1.49 and 1.45 (9H, 2xs).

Example 105.

1-*tert*-Butyl 5-isopropyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate

From Intermediate 1 (160mg) and Intermediate 9 (190mg). Purification by preparative HPLC (Method A) afforded the title compound as a single diastereomer as a pale orange solid (137mg, 42%). TLC R_f 0.51 (EtOAc). LCMS 501 $[M+H]^+$, RT 3.66 mins. ^1H NMR 300MHz (d_4-MeOH) 8.21 (1H, s), 8.19 (1H, s), 7.36 (1H, s), 6.40 (1H, s); 5.14-5.02 (1H, hep), 4.46-4.39 (1H, m), 4.07-4.03 (1H, d), 3.99 (3H, s), 3.73-3.68 (1H, d), 3.13 (3H, s), 3.03-2.88 (1H, m), 2.32-2.20 (1H, m), 1.49 and 1.45 (9H, 2xs), 1.34-1.31 (3H, d), 1.25-1.22 (3H, m).

Example 106.

1-(*tert*-Butoxycarbonyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylic acid

To a solution of Example 104 (100mg), in THF (3ml) and water (3ml), stirring at room temperature was added $LiOH.H_2O$ (9mg). The reaction mixture was

stirred for 2.5 hours before being concentrated *in vacuo*, neutralised with aqueous 1M HCl solution and extracted with EtOAc (3x20ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the title compound as a single diastereomer as an off-white solid 50.5mg (52%). HPLC RT 2.78. LCMS 459 $[M+H]^+$, RT 2.84 mins. ^1H NMR 300MHz (d_4-MeOH) 8.19 (1H, s), 8.17 (1H, s), 7.35 (1H, s), 6.37 (1H, s), 4.45-4.36 (1H, m), 4.00-3.93 (4H, m), 3.74-3.63 (1H, m), 3.10 (3H, s), 3.03-2.97 (1H, m), 2.33-2.22 (1H, m), 1.47-1.40 (9H, m).

Examples 107 and 108 describe the preparation of two out of the four diastereomers of *tert*-butyl 7'-methoxy-3'-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate.

Example 107.

***tert*-Butyl 7'-methoxy-3'-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate (Diastereomer 1)**

To a solution of (*1Z*)-*N'*-hydroxyethanimidamide (CAS 140461-42-3) (20mg) in dry THF (5ml) under nitrogen was added sodium hydride (60% dispersion in mineral oil, 11mg) and the mixture heated at reflux for 90 mins. A solution of Example 104 was then added and the reaction mixture heated at reflux for 18 hours. The mixture was concentrated *in vacuo* and H_2O (30ml) added to the residue. This was extracted with DCM (2x75ml) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*, to give a mixture of two diastereomers. Purification by column chromatography on silica eluting with EtOAc followed by preparative HPLC (Method A) afforded Diastereomer 1 as a white solid (4.8mg, 9%). TLC R_f 0.29 (EtOAc). LCMS 498 $[M+H]^+$, RT 3.28 mins. ^1H NMR 300MHz (d_4-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.38 (1H, s), 6.38 (1H, s, br), 5.31-5.28 (1H, dd), 4.19-4.15 (1H, d), 3.98 (3H, s), 3.83-3.79 (1H, d), 3.18 (3H, s), 3.18-3.03 (1H, m), 2.50-2.37 (1H, m), 2.45 (3H, s), 1.50 and 1.35 (9H, 2xs).

Example 108.

***tert*-Butyl 7'-methoxy-3'-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate (Diastereomer 2).**

Following the procedure described for Example 107; Diastereomer 2 was also isolated as an off-white solid (1.5mg, 3%). TLC R_f 0.18 (EtOAc). LCMS 498 $[M+H]^+$, RT 3.13 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (2H, 2xs), 7.38 (1H, s), 6.54 (1H, s), 5.34-5.25 (1H, m), 4.01 (3H, s), 3.98 (2H, s), 3.16 (3H, s), 2.76-2.73 (1H, m), 2.40 (3H, s), 1.40 and 1.25 (9H, 2xs).

Example 109.

***tert*-Butyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-5-(pyrrolidin-1-ylcarbonyl)-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirring solution of Example 106 (44mg), HBTU (36mg), and DIPEA (0.09ml) in DMF (2ml) was added pyrrolidine (0.02ml). The reaction mixture was stirred at room temperature for 18 hours concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with 2% MeOH/DCM, to yield the title compound as a single diastereomer as a solid 18mg (37%). TLC R_f 0.24 (2%MeOH/DCM). LCMS 512 $[M+H]^+$, RT 3.14 mins. ^1H NMR 300MHz (d_4-MeOH) 8.17 (1H, s), 8.15 (1H, s), 7.34 (1H, s), 6.43 (1H, s), 4.73-4.66 (1H, m), 3.98 (3H, s), 3.86-3.35 (6H, m), 3.12 (3H, s), 3.05-2.92 (1H, m), 2.22-2.11 (1H, m), 2.05-1.85 (4H, m),1.45-1.35 (9H, m).

Example 110.

***tert*-Butyl 5-[(dimethylamino)carbonyl]-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1-carboxylate**

To a stirring solution of Example 106 (70mg), EDC (29mg), HOBt (21mg) and TEA (0.06ml) in DCM (5ml), was added dimethylamine hydrochloride (25mg). The mixture was stirred at room temperature overnight. More dimethylamine hydrochloride (25mg) and TEA (0.03ml) were added to the reaction mixture, which was left to stir at room temperature overnight. DMAP (1mg) was added to the reaction mixture, which was left to stir at room temperature overnight. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with 4%MeOH/DCM to yield the title compound as a single diastereomer as a white solid 5.3mg (7%). HPLC RT

2.92 minutes. LCMS 486 $[M+H]^+$, RT 2.92 mins. ^1H NMR 300MHz (d_6-DMSO, 130°C) 8.13 (1H, s), 7.99 (1H, s), 7.25 (1H, s), 7.23 (1H, s, br), 6.35 (1H, s), 4.87-4.80 (1H, m), 3.94 (3H, s), 3.93-3.90 (1H, d), 3.66-3.63 (1H, d), 3.05 (3H, s), 3.00 (6H, s), 2.95-2.90 (1H, m), 2.10-2.05 (1H, m),1.40 (9H, m).

Example 111.

Methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate hydrochloride

To a solution of Example 104 in dry DCM (2ml) under nitrogen cooled to 0°C was added a solution of HCl in Et_2O (1.0M, 20ml). The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The resulting solid was filtered off, washed with copious quantities of Et_2O and dried *in vacuo* to afford the title compound as a single diastereomer as an off-white solid (80mg, 92%). LCMS 373 $[M-HCl+H]^+$, RT 1.50 mins. ^1H NMR 400MHz after aqueous $NaHCO_3$ shake. ($CDCl_3$) 8.31 (1H, s), 7.88 (1H, s), 7.38 (1H, s), 6.18 (1H, s), 4.02-3.97 (1H, m), 3.95 (3H, s), 3.78 (3H, s), 3.36-3.33 (1H, d), 3.30-3.27 (1H, d), 2.58-2.52 (1H, m), 2.26-2.22 (2H, d).

Example 112.

Methyl 1-(2-furoyl)-7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate

To a solution of 2-furoic acid (13mg) in DCM (5ml) stirring under nitrogen at room temperature was added EDC (23mg), TEA (0.06ml) and HOBt (16.2mg). The mixture was stirred at room temperature for 30 minutes before adding Example 10 (49mg). The reaction mixture was allowed to stir at room temperature for another 48 hours. DMAP (2mg) was added and the mixture stirred for 18 hours and concentrated *in vacuo*. Purification was by preparative HPLC (Method B) followed by column chromatography on silica eluting with 4% MeOH/DCM to give the title compound as a single diastereomer as a white solid (2.5mg, 4.5%). TLC R_f 0.15 (4% MeOH/DCM). LCMS 467 $[M+H]^+$, RT 2.65 mins. ^1H NMR 300MHz (d_4-MeOH) 8.20 (2H, s), 7.74 (1H, s), 7.35 (1H, s) 7.20 (1H, m), 7.12 (1H, d), 6.53 (1H, m), 6.60 (1H, m), 6.38 (1H, s) 4.90-4.80 (1H, m), 4.58-4.50 (1H d), 4.37-4.30 (1H, d), 4.00 (3H, s), 3.80 (3H, s), 3.15 (3H, s) 3.05-2.95 (1H, m), 2.35-2.25 (1H, m).

Example 113.

1-Ethyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate

To a solution of Example 111 (49mg) in DCM (5ml), stirring under nitrogen at 0°C was added TEA (0.05ml) followed by ethylchloroformate (0.013ml). The mixture was allowed to warm slowly to room temperature. The reaction mixture was diluted with water ((20ml) and extracted into DCM (3x50ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 2% MeOH/DCM afforded the title compound as a single diastereomer as an off-white solid (35.7mg, 67%). HPLC RT 2.77 mins. LCMS 445 $[M+H]^+$, RT 2.79 mins. ^1H NMR 300MHz (d_4-MeOH) 8.18 (1H, s), 8.15 (1H, s), 7.34 (1H, s) 6.34 (1H, s), 4.58-4.50 (1H, m), 4.20-4.05 (3H, m), 3.98 (3H, s) 3.77 (3H, m), 3.76-3.70 (1H d), 3.10 (3H, s), 3.02-2.90 (1H, m), 2.35-2.24(1H, m), 1.30-1.15 (3H, m).

Example 114 was prepared in a similar manner to the method of Example 12:-

Example 114.

1-*iso*-Propyl 5-methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate

From Example 111 (50mg) and *iso*-propylchloroformate. The residue was purified by column chromatography on silica eluting with 2% MeOH/DCM to yield the title compound as a single diastereomer as a yellow solid, (41.7mg, 62%). HPLC RT 2.99 mins. LCMS 459 $[M+H]^+$, RT 3.01 mins. ^1H NMR 300MHz (d_4-MeOH) 8.17 (2H, 2xs), 7.33 (1H, s), 6.39 (1H, s) 4.92-4.82(1H, m), 4.55-4.47 (1H, m), 4.12-4.02 (1H, d), 3.97 (3H, s), 3.79 (3H, s), 3.75-3.69 (1H, d), 3.11 (3H, s), 3.01-2.89 (1H, m), 2.35-2.22(1H, m), 1.27-1.22 (6H, m).

Example 115.

Methyl 7'-methoxy-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-1-(piperidin-1-ylcarbonyl)-3',4'-dihydro-*1'H*-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate

To a suspension of Example 111 (65mg) in dry DCM (10ml) under N_2 cooled to 0°C was added dropwise 1-piperidinecarbonyl chloride (0.024ml) followed

by TEA (0.05ml), again dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with 5% MeOH/DCM to afford the title compound as a single diastereomer as a pale yellow solid (50mg, 65%). LCMS 484 $[M+H]^+$, RT 2.85 mins. ^{1}H NMR 300MHz (d_4-MeOH) 8.22 (1H, s), 8.20 (1H, s), 7.40 (1H, s) 6.46 (1H, s), 4.85-4.78 (1H, tr), 4.01-3.95 (1H, d), 3.99 (3H, s), 3.82-3.76 (1H, d), 3.78 (3H, s), 3.40-3.20 (2H, m), 3.12-3.01 (1H, m), 3.07 (3H, s), 2.30-2.23 (1H, dd), 1.72-1.50 (6H, m).

Example 116.

Methyl 7'-methoxy-3'-methyl-1-{[methyl(phenyl)-amino]carbonyl}-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate

To a solution of *N*-methylaniline (0.01ml) and pyridine (0.03ml) in DCM (5ml), stirring under nitrogen at –78°C, was added triphosgene (17mg). The reaction mixture was stirred at 0°C for 30 minutes before adding Example 111 (50mg) and pyridine (0.03ml). The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was purified by column chromatography on silica eluting with EtOAc followed by 5% MeOH/DCM to yield the title compound as a single diastereomer as a white solid, (6.4mg, 10%). TLC Rf 0.41 (EtOAc). LCMS 506 [M+H]+, RT 2.91 mins. ^{1}H NMR 300MHz (d_6-DMSO) 8.33 (1H, s, br), 7.88 (1H, s), 7.40-7.12 (8H, m), 6.24 (1H, s), 4.65-4.75(1H, m), 4.85(3H, s), 3.70 (3H, s), 3.58-3.50 (1H, d), 3.13 (3H, s), 3.98-2.78 (5H, s), 2.05-1.93 (1H, m).

Example 117 was prepared in a similar manner to the method of Example 116:-

Example 117.

Methyl 7'-methoxy-1-{[methoxy(methyl)amino]carbonyl}-3'-methyl-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1'H*-spiro[pyrrolidine-3,2'-quinazoline]-5-carboxylate

From Example 111 (50mg) and *N,O*-dimethylhydroxylamine hydrochloride (14mg). Purification by column chromatography on silica eluting with 2% MeOH/DCM afforded the title compound as a brown solid, 14.4mg (21%).

HPLC RT 2.53 minutes. LCMS 460 [M+H]+, RT 2.57 minutes. ^{1}H NMR 300MHz (d_4MeOD) 8.20 (1H, s, br), 8.18 (1H, s), 7.38 (1H, s, br), 6.40 (1H, s) 4.73-4.65(1H, m), 4.23-4.16 (1H, d), 4.00 (3H, s), 3.90-3.86 (1H, d), 3.76 (3H, s), 3.62 (3H, s), 3.11 (3H, s), 3.05 (3H, s), 3.03-2.96(1H, m), 2.25-2.17 (1H, m).

Example 118 describes the preparation of a mixture of two out of the four diastereomers of 1-*tert*-butyl 5-methyl 7'-methoxy-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate, and was prepared in a similar manner to the method of example 104:-

Example 118.

1-*t*ert-Butyl 5-methyl 7'-methoxy-6'-(1,3-oxazol-5-yl)-4'-oxo-3',4'-dihydro-*1H,1'H*-spiro[pyrrolidine-3,2'-quinazoline]-1,5-dicarboxylate

From Intermediate 2 (193mg) and 1-*tert*-butyl 2-methyl (*2S*)-4-oxopyrrolidine-1,2-dicarboxylate (211mg). The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to yield the title compound as a beige solid (297mg, 78%). TLC Rf 0.32 (5% MeOH/DCM). LCMS 459 [M+H]+, RT 3.38 mins. ^{1}H NMR 400MHz (d_4 MeOH) 8.16 (1H, s), 8.13 (1H, s), 7.34 (1H, s), 6.45 and 6.39 (1H, 2xs), 4.43-4.51 (1H, m), 3.99 (3H, s), 3.76-3.79 (4H, m), 3.51-3.58 (1H, m), 2.60-2.70 (1H, m), 2.19-2.29 (1H, m), 1.44 and 1.40 (9H, 2xs).

The ability of the compounds of the invention to inhibit the IMPDH enzymes may be determined using the following assays:

Abbreviations used:

IMPDH Inosine 5'monophosphate dehydrogenase

IMP Inosine 5'monophosphate XMP Xanthosine 5'-monophosphate

NAD β- Nicotinamide adenine dinucleotide

NADH β- Nicotinamide adenine dinucleotide, reduced form

MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

Assay Protocol 1

IMPDH catalyses the NAD dependent oxidation of IMP to XMP with concomitant reduction of the coenzyme. IMPDH activity was determined by

monitoring the production of the fluorescent product, NADH. Assays were performed in a final volume of 200μl containing IMPDH (2μg), NAD (100μM), IMP (100μM), 1% DMSO, 30mM KCl and 100mM Tris/HCl, pH7.5. Fluorescence (excitation 340nm / emission 465nm) was read continuously at 25°C for 30 minutes. From this data, initial rates (i.e. change in fluorescence intensity per minute) were calculated. To determine the IC_{50} values, test compounds were prepared at an initial concentration of 1.0mM in 100% DMSO, then diluted in assay buffer to 0.2mM. Further dilutions were made in assay buffer containing 20% DMSO, prior to diluting 20-fold into the assay, to allow testing across the range 0.3nM to 10μM.

The functional effect of the compounds of the invention may be demonstrated using the following assay:

PBMC Proliferation Assay

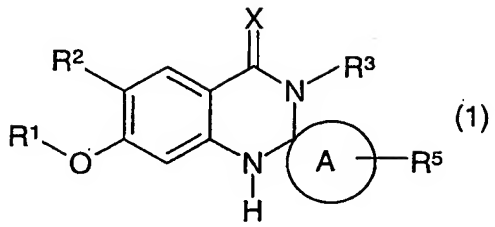
Peripheral blood mononuclear cells were isolated from freshly taken human blood using standard procedures. Cells were plated out in RPMI medium containing 5% human serum in the presence and absence of inhibitor. PHA (25μl of 30μg/ml solution to each well) was added and the plates were incubated at 37°C in an atmosphere of 95% air/5% CO_2 for 48 hours. 0.5μCi of tritiated thymidine was added to each well and the plates were incubated for a further 18 hours. The contents of the plate were transferred to a filter plate and the cells washed with saline. The plates were dried, microscintillation fluid was added to each well and the plate was counted on a scintillation counter. IC_{50} values were calculated by plotting inhibitor concentration versus %inhibition.

The assay described above can be carried out using anti-CD3 (40μl of 3750ng/ml concentration to each well) stimulation instead of PHA.

Compounds of each of the Examples inhibit IMPDH enzymes with IC_{50} values of 5μM or below.

CLAIMS

1. A compound of formula (1):



(1)

wherein:

X is an oxygen or sulfur atom;

R^1 is an aliphatic, cycloaliphatic or cycloalkyl-alkyl- group;

R^2 is an optionally substituted heteroaromatic group or a –CN group;

R^3 is a group $-(Alk^1)_mL^1(Alk^2)_nR^4$ in which m and n, which may be the same or different, is each zero or the integer 1, Alk^1 and Alk^2, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^1 is a covalent bond or a linker atom or group and R^4 is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

A is an optionally substituted cycloaliphatic or heterocycloaliphatic group optionally fused to an optionally substituted aryl or heteroaryl group;

R^5, which may be attached to any available C or N atom present in the cycloaliphatic or heterocycloaliphatic, or where fused, aryl or heteroaryl group, is a group $-(Alk^3)_tL^2(Alk^4)_vR^6$ in which t and v, which may be the same or different, is each zero or the integer 1, Alk^3 and Alk^4, which may be the same or different, is each an optionally substituted aliphatic or heteroaliphatic chain, L^2 is a covalent bond or a linker atom or group and R^6 is a hydrogen or halogen atom or a –CN group or an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

2. A compound according to Claim 1 in which Alk^1, Alk^2, Alk^3 or Alk^4, when present in compounds of formula (1), may be the same or different, and is each an optionally substituted C_{1-6} alkylene chain.

3. A compound according to Claim 1 or Claim 2 wherein R^3 is a group $-(Alk^1)_mL^1(Alk^2)_nR^4$ and R^5 is a group $-(Alk^3)_tL^2(Alk^4)_vR^6$ in which L^1 or L^2 is covalent bond or an atom or group selected from –O- or -S- atoms or –C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, -C(O)O-, -OC(O)-, $-N(R^7)-$ [where R^7 is a hydrogen atom or a straight or branched C_{1-6}alkyl group], $-CON(R^7)-$, $-CSN(R^7)-$, $-N(R^7)CO-$, $-N(R^7)CS-$, $-S(O)_2N(R^7)-$ or $-N(R^7)S(O)_2-$ groups.

4. A compound according to any one of Claims 1 - 3 in which R^3 is the group $-Alk^1-L^1-R^4$.

5. A compound according to any one of Claims 1 – 4 in which R^3 is a C_{1-6} alkyl group.

6. A compound according Claim 5 in which R^3 is a methyl group.

7. A compound according to any one of Claims 1 - 4 in which R^3 is a hydrogen atom.

8. A compound according to any one of Claims 1 - 7 in which X is an O atom.

9. A compound according to any one of Claims 1 - 8 wherein R^1 is a C_{1-6} alkyl group.

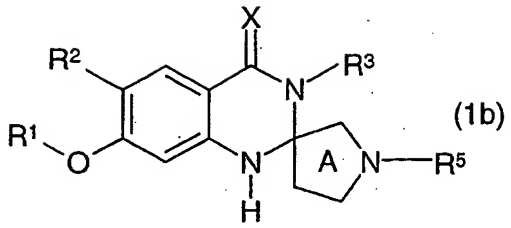
10. A compound according to Claim 9 wherein R^1 is a methyl group.

11. A compound according to any one of Claims 1 - 10 wherein R^2 is a five-membered heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen.

12. A compound according to Claim 11 wherein R^2 is an oxazolyl group.

13. A compound according to any one of Claims 1 – 12 wherein A is optionally substituted C_{3-6} cycloaliphatic group or 3 to 6 membered saturated monocyclic hydrocarbon ring system containing one or two L^4 linker atoms or groups, optionally fused to an optionally substituted phenyl or monocyclic C_{1-9}heteroaromatic group containing one, two, three or four heteroatoms selected from oxygen, sulfur or nitrogen.

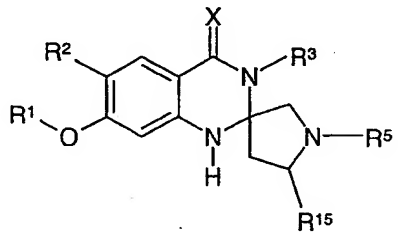
14. A compound according to any one of claims 1 – 13 which has the formula (1b):



(1b)

in which A is an optionally substituted pyrrolidinyl ring; R^1, R^2, R^3, R^5 and X are as defined herein.

15. A compound according to any one of claims 1- 14 which has the formula (1c):



(1c)

wherein R^1, R^2, R^3, R^5 and X are defined herein; R^{15} is a group selected from –CN, $-CO_2R^{10a}$ [where R^{10a} is a hydrogen atom or a C_{1-6}alkyl group], -AlkOR^{10a} [where Alk is a C_{1-3}alkylene chain], $-NR^{10a}COR^{16}$ [where R^{16} is a C_{1-6}alkyl group], $-NR^{10a}SO_2R^{16}$, $-SO_2R^{16}$, $-COR^{16}$, $-CONR^{17}R^{18}$ [where R^{17} and R^{18}, which may be the same or different, is each a hydrogen atom or a C_{1-6}alkyl group, or R^{17} and R^{18} may join together to form a 4 to 6 membered heterocycloalkyl group], $-NR^{17}R^{18}$, $-SO_2NR^{17}R^{18}$, C_{1-6}alkyl, haloC_{1-6}alkyl or 5 or 6 membered heteroaryl group.

16. A pharmaceutical composition comprising a compound according to any of Claims 1 to 14 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

17. A compound according to any of Claims 1 to 14 for use in the treatment of cancer, inflammatory disorders, autoimmune disorders, psoriatic disorders and viral disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/03878

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/04 C07D239/70 C07D471/10 C07D487/10 C07D491/10
A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 14686 A (ASTRA) 24 April 1997 (1997-04-24) page 0; claims	1,14,16, 17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2003	02/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 03/03878

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9714686 A	24-04-1997	AU 704133 B2	15-04-1999
		AU 7224396 A	07-05-1997
		BR 9610988 A	06-04-1999
		CA 2235304 A1	24-04-1997
		CZ 9801193 A3	16-09-1998
		EE 9800116 A	15-10-1998
		EP 0858451 A1	19-08-1998
		WO 9714686 A1	24-04-1997
		HU 9900028 A2	28-04-1999
		JP 11513679 T	24-11-1999
		NO 981710 A	03-06-1998
		NZ 319673 A	23-06-2000
		PL 326353 A1	14-09-1998
		SK 45898 A3	11-01-1999
		TR 9800697 T2	21-07-1998
		US 5883102 A	16-03-1999
		ZA 9608767 A	17-04-1997